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(54) Amino acid sequences of anti-idiotypic antibodies against anti-cancer human monoclonal antibody, and dna base sequences encoding those sequences

(57) Amino acid sequences of the H chain and L chain variable regions of mouse monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 against idiotypes of a cancer cell antigen-specific human immunoglobulin CLN/IgG produced by a human/human fused cell strain CLN/SUZ H11, and base sequences of the genes of the variable regions are disclosed.

The above amino acid sequences and the base sequences are useful in medical and pharmaceutical fields such as prophylaxis, treatment and/or diagnosis of human diseases, and/or in pharmacological and/or biochemical fields, etc. such as biochemical reagents, and reagents for purification of biomacromolecules.

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Description**Detailed Description of the Invention**

5 This invention relates to the structure of the variable regions of mouse immunoglobulins against idiotypes of an antigen-specific human immunoglobulin, useful in wide fields, for example in pharmaceutical fields such as prophylaxis, treatment and/or diagnosis of human diseases, and/or in pharmacological and/or biochemical fields such as biochemical reagents and reagents for purification of biomacromolecules.

10 More detailedly, this invention relates to the amino acid sequences of the H chain and L chain variable regions of mouse immunoglobulins against idiotypes of a cancer cell antigen-specific human immunoglobulin produced by a human/human fused cell strain CLN/SUZ H11 from a B cell of a patient carrying human cervical carcinoma and a human lymphoblastoid cell strain, and relates to the base sequences of the genes of the variable regions.

15 Since the development of the technique of formation of monoclonal antibodies by cell fusion or immortalization of cells, many useful antibodies have been obtained using mainly mice. Among them, monoclonal antibodies against malignant tumor cells are utilized not only for fundamental researches such as analyses of tumor antigens, but in serum diagnoses, image diagnoses of tumors using labeled antibodies, and have extremely high utilization value. Particularly, human-derived anti-cancer monoclonal antibodies are expected as ideal antibodies in the clinical field, since they have only faint or no side effects.

20 In such circumstances, one of the present inventors, as disclosed detailedly in Japanese Laid-Open Patent Publication No. 201994/1983 (= U. S. Patent No. 5,286,647; EP-A-839,02157.3), Japanese Laid-Open Patent Publication No. 135898/1984 and Japanese Laid-Open Patent Publication No. 137497/1984, established a cell strain CLN/SUS H11 (ATCC No. HB 8307) which produces a human monoclonal antibody having a high reactivity with human cancer cells. Interesting findings are obtained about the antibody (named CLN-IgG) produced by this cell strain, that the antibody class is IgG; the isotypes are $\gamma 1$ type and κ type; and the antibody binds to a cancer antigen immunohistologically existing 25 on the surface of the cancer cells and moreover inhibits proliferation of the cancer cells. At present, the whole amino acid sequence and DNA base sequence of the antibody are clarified (Japanese Laid-Open Patent Publication No. 346792/1992 = WO 92/20799).

30 On the other hand, since Jerne put forward the so-called network theory, various researches have been made on the structure of the variable regions of antibodies. An antibody binds to an antigen at its variable region (antigen combining site). Therefore, the variable regions of antibodies have various three-dimensional-like structures in accordance with the structures of the antigenic determinants on the surfaces of antigens to be recognized. Thus, an antibody itself can be considered to be an antigen, and in the case, the structures of the variable regions of the antibody are called idiotypes, and antibodies against the idiotypes of the antibody are called anti-idiotypic antibodies. The structure corresponding to an antigenic determinant is called an idioype. An idioype can be thought to be an aggregate of idiotypes. It was reported 35 that among anti-idiotypic antibodies (Ab2) against an antibody (Ab1) exist antibodies which competitively inhibit binding of Ab1 to an antigen and have idiotypes analogous to antigens recognized by the antibodies, i.e. antibodies having structures as so-called internal images of the antigen.

40 In view of the above findings, anti-idiotypic antibodies are expected to be utilized for the purpose of treatment and/or diagnosis of cancers.

45 For example, as for the purpose of cancer treatment, a vaccine therapy using an anti-idiotypic antibody as an antigen is made possible. It is generally difficult to get cancer antigens in large amounts, and it is restricted from a safety aspect and an ethical aspect to directly immunize human beings with cancer cells as antigens. Therefore, these problems can be avoided by performing immunization with an anti-idiotypic antibody in place of an antigen.

50 In a diagnostic aspect, anti-idiotypic antibodies can be utilized to examine the state of immune reactions against cancer cells. Specifically, it serves for early detection of cancers, judgment of therapeutic effects to detect or determine one's antibodies against cancer antigens existing in the blood or humor of cancer patients.

Under such technical background, problems as stated below are underlying to be solved.

55 1) When anti-idiotypic antibodies are utilized as vaccines or diagnostic drugs, it is necessary to provide these antibodies in large amounts and stably. 2) There is a possibility to give more powerful vaccines or diagnostic drugs abounding in functionality by altering or modifying the antibodies.

A method by gene manipulation is considered as a means for solving the above problems, i.e. a means for realizing improvement of production amount of the antibodies and elevation or modification of the activities of the antibodies.

For example, in the case of the problem of 1), it can be considered to solve the problem by cloning such an antibody gene, introducing the gene into host cells such as animal cells or *Escherichia coli*, expressing the antibody gene to give a large amount of the antibody, and in the case of the problem of 2), it can be considered to alter such an antibody so as to have stronger immunogenicity by artificially changing the antibody gene, or to design an antibody molecule having a higher vaccinal activity by adding a function which the antibody does not inherently have, for example an enzymatic activity, an immunity induction activity or the like to the antibody molecule or a fragment thereof.

For accomplishment of these purposes, separation of anti-idiotypic antibody genes, and clarification of their structures are necessary. However, there has not so far been known anything at all about the structures of L chains and H chains constituting anti-idiotypic antibodies against idiotypes of CLN-IgG, and the gene structures of the variable regions having a function to specifically bind to idiotypes of CLN-IgG.

5 Thus the main object of this invention is to clarify the gene structures of the L chains and the H chains of anti-CLN-IgG idiotype antibodies.

The present inventors have succeeded in creating hybridomas producing, respectively, five kinds of mouse anti-CLN-IgG idiotype antibodies (Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33) having $\gamma 1$ and κ isotypes against the idiotypes of CLN-IgG; have separated, from the hybridomas, cDNAs encoding the L chains and H chains of the anti-idiotypic 10 antibodies, respectively; have clarified their DNA base sequences; have determined, based on these sequences, the amino acid sequences of the L chains and H chains of the antibodies, respectively; and have completed this invention.

Thus, according to this invention are provided an immunoglobulin H chain variable region fragment which contains a hypervariable region CDR1 having an amino acid sequence selected from

15

(1) Ser Tyr Trp Met His;
Asp Tyr Tyr Met Asn; and
Asn Tyr Trp Met Gln,

20

a hypervariable region CDR2 having an amino acid sequence selected from

25

(2) Ala Ile Tyr Pro Gly Asn Ser
Asp Ile Ser Tyr Ser Gln Asn
Phe Lys Asp;
Phe Ile Arg Asn Lys Ala
Asn Leu Tyr Thr Thr Asp
Tyr Ser Ala Ser Val Lys
Gly;
Phe Ile Arg Asn Lys Ala
Asn Tyr Tyr Thr Thr Glu
Tyr Ser Ala Ser Val Lys
Gly; and
Ala Ile Tyr Pro Gly Asp
Gly Asp Thr Arg Tyr Thr
Glu Lys Phe Lys Gly,

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and a hypervariable region CDR3 having an amino acid sequence selected from

5 (3) Glu Glu Tyr Asp Tyr Asp
Thr Leu Asp Tyr;
Asp Arg Gly Gly Arg Asp
Trp Tyr Phe Asp Val;
Asp Gly Phe Leu Arg Asp
Trp Tyr Phe Asp Val; and
10 Ser Gly Tyr Tyr Gly Ser
Phe Val Gly Phe Ala Tyr;
15

and DNA and RNA fragments encoding the immunoglobulin H chain variable region fragment.

According to this invention are further provided an immunoglobulin L chain fragment which contains a hypervariable
20 region CDR1 having an amino acid sequence selected from

25 (1) Tyr Arg Ala Ser Lys Ser Val
Gln Leu His Leu Ala Ile Val
Tyr Met His;
Tyr Arg Ala Ser Lys Ser Val
Ser Thr Ser Gly Tyr Ser Tyr
30 Met His;
Lys Ala Ser Gln Asp Val Asn
Thr Ala Val Ala; and
Lys Ala Ser Gln Asp Val Thr
35 Thr Asp Val Ala

40 a hypervariable region CDR2 having an amino acid sequence selected from

45 (2) Leu Val Ser Asn Leu Glu Ser;
Leu Val Ser Asn Leu Asp Ser; and
Ser Ala Ser Tyr Arg Tyr Thr,

50

55

and a hypervariable region CDR3 having an amino acid sequence selected from

(3) Gln His Ile Arg Val Ala Tyr
 5 Thr;
 Gln His Ile Arg Gly Ala Tyr
 10 Thr;
 Gln His Ile Glu Gly Ala Tyr
 15 Thr;
 Gln Gln His Tyr Ser Pro Pro
 Leu Thr; and
 Gln Gln His Tyr Ser Thr Ala
 20 Trp Thr;

20 and DNA and RNA fragments encoding the immunoglobulin L chain variable region fragment.

In this invention, cytoplasmic RNAs were prepared from the five mouse hybridomas, respectively; the RNAs were converted to cDNAs by a reverse transcriptase; the antibody genes were amplified using these cDNAs as templates and using the PCR method; the amplified DNA fragments were integrated into plasmids and cloned; the base sequences of the insertion DNAs of the plasmids purified from Escherichia coli clones isolated were determined, and the amino acid sequences were determined based on the base sequences. These steps are further detailedly described below.

[1] Isolation of cytoplasmic RNAs

Each mouse hybridoma is cultured and proliferated in a culture medium, e.g. and RDF or RPMI 1640 medium, 30 containing 5% fetal bovine serum under a suitable condition, e.g. under a condition of 37°C and a carbon dioxide concentration of 5%; the resultant cells are collected by centrifugation; and the cytoplasmic RNA is extracted from the cells by a conventional method, e.g. a method disclosed in 7.12 of Molecular Cloning (2nd edition, edited by Sambrook et al., Cold Spring Harbor Laboratory Press 1989). The resultant cytoplasmic RNA can further be utilized as a template for cDNA synthesis. Specifically in this invention, the cytoplasmic RNAs were extracted from mouse hybridomas No. 3, No. 17, No. 20, No. 27 and No. 33, and provided for synthesis of cDNAs.

[2] Synthesis of cDNAs

Using a cytoplasmic RNA obtained in the step of [1] as a template, a single-strand DNA complementary to the 40 mRNA is synthesized in the presence of dATP, dGTP, dTTP and dCTP using, as a primer, an oligo dT corresponding to a poly A, or a synthetic nucleotide having a random sequence, and a reverse transcriptase. In the specific operations in the invention, cDNAs were synthesized using the cytoplasmic RNAs obtained in the step of [1] as templates and a random hexamer as a primer, respectively, and provided for the step of amplification of the antibody genes.

45 [3] Amplification of antibody genes by PCR

PCR reaction is performed in the presence of dATP, dGTP, dTTP, dCTP and Taq polymerase using as a template a single-strand cDNA obtained in the step of [2] and as a primer a sequence of the antibody gene (e.g., a sequence encoding a constant region, a variable region or a leader region of the antibody gene) to amplify the antibody gene. 50 Suitably in the invention, the antibody genes were amplified using as templates the single-strand cDNAs obtained in the step of [2] and using synthetic DNA oligomers corresponding to the sequences of the leader regions and variable regions of the L chains and H chains of the antibodies, respectively.

[4] Cloning of PCR-amplified DNA fragments

55 A PCR-amplified DNA fragment obtained in the step of [3] is, directly or after treatment with restriction enzyme(s), ligated into one of various vectors, for example plasmid vectors such as pUC 18, pCR1000 and pCR™, phage vectors such as M 13 phage, and phagemid vectors such as pUC 118 and pBluescript SK' to prepare a vector containing the insertion fragment. Then, Escherichia coli is transformed with the vector, and a colony of the Escherichia coli containing

the targeted antibody gene fragment is obtained. The purified vector recovered from the Escherichia coli is provided as a sample for determination of the DNA base sequence. In the specific operations in the invention, the PCR-amplified DNA fragments obtained in the step of [3] were directly ligated, respectively, into pCR1000 and pCR™ plasmid vector; an Escherichia coli INVαF' was transformed with each of the resultant plasmids; and the plasmids were purified from the resultant Escherichia coli colonies, respectively.

[5] Determination of the base sequences and amino acid sequences of the DNAs

The base sequence of the DNA at the insertion site in a plasmid obtained in the step of [4] can be determined using the Maxam-Gilbert method or the Sanger method. In the invention, the pCR1000 or pCR™ plasmid vectors containing the insertion fragments were purified, respectively; their base sequences were determined by the Sanger method; and the amino acid sequences were presumed based on their base sequences, respectively.

Hereafter, this invention is further specifically described below according to examples.

Drawings referred to in Examples are briefly described as follows.

Fig. 1 is a drawing showing isotypes of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33.

Fig. 2 is a drawing showing the monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 specifically bind to CLN-IgG, and do not bind to other human IgGs.

Fig. 3 is a drawing showing that monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 are competitively inhibiting the binding between CLN-IgG and human matrical carcinoma cell ME-180.

Fig. 4 is a drawing where the amino acid sequences of the H chain variable regions of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 are notated in parallel according to the Kabat's notation, and the regions of the hypervariable regions CDR1, CDR2 and CDR3 are determined.

Fig. 5 is a drawing where the amino acid sequences of the L chain variable regions of monoclonal antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 are notated in parallel according to the Kabat's notation, and the regions of the hypervariable regions CDR1, CDR2 and CDR3 are determined.

Example 1: Preparation of mouse hybridomas

100 µl of 1 mg/ml human IgG (produced by Cappel) is intraperitoneally injected to a Balb/c mouse on the first day after its birth to prepare a mouse having immunological tolerance to human IgG. Six weeks later, the mouse is immunized as follows with CLN-IgG as an antigen.

CLN-IgG purified from a culture medium of a human/human hybridoma CLN/SUZ H11 (ATCC No. HB8307) according to an ammonium sulfate precipitation method and protein A-affinity chromatography was adjusted to a concentration of 2 µg/µl with physiological saline; an equal amount of complete Freund's adjuvant solution was added; and after mixing and emulsification, 100 µl of the emulsion (corresponding to 100 µg of CLN-IgG) was subcutaneously injected into the immunologically tolerated mouse. Thereafter, similar immunization was repeated 4 to 5 times, the murine spleen was enucleated 4 days after the final immunization and made to be spleen cells, and they were used for the following cell fusion.

A mouse parent cells NS-1 (ATCC TIB 18) and the spleen cells are washed with portions of RPMI 1640 medium not containing serum, respectively, and the both of the cells are mixed and centrifuged. 1 ml of 50% polyethylene glycol (average molecular weight : 4,000) is added dropwise to the resultant precipitate over a period of 1 minute. 10 ml of RPMI 1640 medium is further added over a period of 3 minutes, the mixture is centrifuged at 400 x g for 5 minutes, the precipitate is suspended in 10 ml of RPMI 1640 medium containing 20% fetal bovine serum, and the suspension is spread into a 96-well microplate.

Thereafter, the cells were cultured in HAT medium for 14 to 21 days, transferred to HT medium, and finally cultured in RPMI 1640 medium containing 10% fetal bovine serum.

The antibody titers in the culture supernatants on the wells where proliferation was observed were assayed by an enzyme-labeled antibody technique; hybridoma clones secreting monoclonal antibodies which bind to CLN-IgG but not to human IgG were obtained from the appropriate wells by the limiting dilution method; and these hybridoma clones were named No. 3, No. 17, No. 20, No. 27 and No. 33.

Example 2: Determination of isotypes of the mouse antibodies

Isotypes of the antibodies secreted from the 5 mouse hybridomas obtained in Example 1 were determined as follows using a mouse monoclonal antibody isotyping kit (produced by Amersham Co.).

The mouse hybridomas are started to be cultured at a concentration each of 5×10^4 /ml in portions of RPMI 1640 medium containing 10% fetal bovine serum, respectively, and 5 days later the culture supernatants are obtained, one stick portions of the typing sticks are placed in test tubes, respectively; 3 ml portions of the culture supernatants 5-fold diluted with TBS-T (Tris-buffered saline (TBS, pH 7.6) containing 0.1% Tween 20) are added thereto respectively; and

the mixtures are incubated at room temperature for 15 minutes. The culture supernatants are discarded, 5 ml portions of TBS-T are added, and the typing sticks are washed at room temperature for 5 minutes. TBS-T was discarded, and the washing was repeated once more. 3 ml portions of a peroxidase-labeled anti-mouse antibody 500-fold diluted with TBS-T are added, and the mixtures are incubated at room temperature for 15 minutes. The typing sticks are washed twice in the same manner as above; 3 ml portions of an enzyme substrate solution (obtained by adding one drop of 30% aqueous hydrogen peroxide to 50 ml of a TBS solution of 4-chloro-1-naphthol) are added; the mixtures are subjected to reaction at room temperature for 15 minutes; and then the sticks are washed with distilled water. The isotypes of the mouse antibodies are determined based on the resultant signals, respectively.

As a result, as shown in Fig. 1, all the isotypes of these antibodies were $\gamma 1$ and κ .

10 Example 3: Examination of specificities of the anti-idiotypic antibodies

It was examined according to a dot blot technique, using an ECL Western blotting detecting reagent (produced by Amersham Co.), that the mouse anti-CLN-IgG idiotype antibodies specifically bind to CLN-IgG. The process is stated below.

CLN-IgG and human IgG1 (produced by Protogen Co.) were diluted with PBS to concentrations of 50 to 0.2 μ l/ml, respectively. 2 μ l portions of the thus prepared samples were spotted on a number of Hybond-ECL nitrocellulose membrane (produced by Amersham Co.), respectively and after being dried, the nitrocellulose membranes were allowed to stand at room temperature for one hour in PBS-T (0.3% Tween 20-containing PBS) containing 5% skim milk. After being washed with PBS-T, the nitrocellulose membranes were allowed to stand at room temperature for one hour in the culture supernatants (500-fold diluted with PBS-T) of mouse hybridomas No. 3, No. 17, No. 20, No. 27 and No. 33, respectively. After being washed with PBS-T, the nitrocellulose membranes were allowed to stand at room temperature for one hour in portions of a peroxidase-labeled sheep anti-mouse Ig antibody 3,000-fold diluted with PBS-T, respectively. After being washed with PBS-T, the nitrocellulose membranes were subjected to reaction for one minute in portions of the ECL detecting reagent, and sheets of X-ray film were exposed for 30 seconds to the light emitted from the resultant nitrocellulose membranes, respectively.

The results of the sheets of X-ray film developed are shown in Fig. 2. Any of the five antibodies bound to CLN-IgG, but did not bind to human IgG1. Namely, it was revealed that these antibodies are specific to CLN-IgG.

Next, it was examined whether or not the mouse antibodies have an activity to inhibit the binding of a human monoclonal antibody CLN-IgG to a human cancer cell. The method is stated below.

A human cervical carcinoma cell ME-180 (available from ATCC) is cultured in DF medium (a 1:1 mixed medium of DME : F-12) containing 10% fetal bovine serum. At the stage when the number of the cells becomes 5×10^6 to 1×10^7 , the cells are detached from the bottom face of the Petri dish using trypsin, collected by centrifugation and sufficiently washed with the medium. A constant number (10⁵/100 μ l) each of the cells is placed in each well of a 96-well microtiter plate, and allowed to stand at 37°C overnight to be attached on the plate. 50 μ l portions of 3% glutaraldehyde solution were added dropwise into the respective wells, and the mixtures are allowed to stand at 37°C for 20 minutes to fix the cells. The cells of each well are centrifuged at 200 $\times g$ for 10 minutes and washed three times with a gelatin buffer (10 mM phosphate-buffered physiological saline containing 0.3% gelatin); 200 μ l portions of 1% bovine serum albumin (BSA) solution are added dropwise; and the mixture is allowed to stand at 37°C for one hour to block the plate. The cells are washed three times with the gelatin buffer to remove BSA not adsorbed. Thereafter, dilutions at various rates (100 to 1,000,000-fold) of the ascites obtained by intraperitoneally inoculating into mice the various hybridomas secreting the mouse anti-idiotypic antibodies are added dropwise together with CLN-IgG (50 μ g each), and the mixtures are subjected to reaction at 37°C for one hour. The cells of these wells are washed three times with the gelatin buffer, 50 μ l portions of a 3,000-fold diluted peroxidase-conjugated goat anti-human Ig antibody (produced by TACO Co.) are added dropwise, respectively, and the mixtures are subjected to reaction at 37°C for 30 minutes. The cells are washed three times with the gelatin buffer, and portions of a substrate solution containing hydrogen peroxide and o-phenylenediamine are added to perform reaction in a darkroom. 10 minutes later, 50 μ l portions of 5N sulfuric acid are added to stop the reaction. When the peroxidase-conjugated goat anti-Ig antibody remains on the microplate, namely when the human IgG to be bound thereto remains, a yellow reaction product having absorption at 490 nm is formed. The amount of CLN-IgG bound to the cancer cell is determined by measuring the amount of the reaction product by a spectrometer.

It was clarified, according to the above method, that all the mouse antibodies Idio 3, Idio 17, Idio 20, Idio 27 and Idio 33 inhibit the binding of CLN-IgG to the cancer cell (Fig. 3).

From the foregoing, these mouse antibodies are antibodies against the idiotypes of CLN-IgG.

55 Example 4: Preparation of RNA

From the five kinds of mouse hybridomas No. 3, No. 17, No. 20, No. 27 and No. 33, the cytoplasmic RNAs were extracted according to the method disclosed in Molecular Cloning (2nd edition, edited by Sambrook et al., Cold Spring Harbor Laboratory Press 1989) 7, 12, as stated below.

10⁸ each of the hybridomas cells are collected by centrifugation, and washed twice with 10 times each precipitate's volume of a phosphate-buffered saline. The cells of these groups are centrifuged at 2,000 x g and 4°C for 5 minutes, and the resultant precipitates are suspended in 200 µl portions of an RNA extracting solution (0.14 M NaCl, 1.5 mM MgCl₂, 10 mM Tris-HCl pH 8.6, 0.5% Nonidet P-40, 1 mM dithiothreitol, 20 mM vanadylribonucleoside complex), respectively. The suspensions are subjected to vortex for 15 seconds and allowed to stand on ice for 5 minutes. The resultant suspensions are centrifuged at 12,000 x g for 30 seconds to remove the cell nuclei as precipitates; to the supernatants are, respectively, added 200 µl portions of a proteinase buffer (0.2 M Tris-HCl pH 8.0, 25 mM EDTA pH 8.0, 0.3 M NaCl, 1.2% SDS) and 1 µl portions of an aqueous proteinase K solution (20 mg/ml); and the mixtures are sufficiently stirred and subjected to incubation at 37°C for 30 minutes. Equal volume portions of phenol/chloroform are added to the reaction 10 solutions, respectively, and the mixtures are stirred, centrifuged at 5,000 x g and room temperature for 10 minutes, and then allowed to separate into organic layers and aqueous layers, respectively. 400 µl portions of isopropanol cooled on ice in advance are added to the aqueous layers recovered, respectively, and the mixtures are allowed to stand on ice for 30 minutes. The mixtures are centrifuged at 12,000 x g and 4°C for 10 minutes to collect RNAs. The resultant RNA 15 precipitates are washed with 1 ml portions of ethanol, dried under reduced pressure and suspended in appropriate amount portions of TE buffer, respectively. Using the cytoplasmic RNAs obtained according to the above operations, the antibody genes are amplified.

Example 5: Amplification and cloning of the antibody genes by the RT-PCR method

20 The antibody genes were amplified from the cytoplasmic RNAs obtained in Example 4, using a GeneAmp® RNA PCR kit (produced by Takara Shuzo Co., Ltd.). First, 20 µl each of reactive solutions were prepared containing PCR buffer II (x1), 5 mM MgCl₂, 1 mM dATP, 1 mM dGTP, 1 mM dTTP and 1 mM dCTP, 1 U/µl an RNase inhibitor, 2.5 µM a random hexamer, 2.5 U/µl a reverse transcriptase and 100 ng each of the above-mentioned cytoplasmic RNAs, respectively; 20 µl portions of a mineral oil were overlaid thereon respectively; and incubations were performed at room 25 temperature for 10 minutes, at 42°C for 15 minutes, at 99°C for 5 minutes and then at 4°C for 5 minutes to perform cDNA synthesis by reverse transcription reaction. Then, 80 µl portions of a solution consisting of 4 µl of 25 mM MgCl₂, 8 µl of 10x PCR buffer II, 65.5 µl of sterile distilled water, 0.5 µl of AmpliTaq DNA polymerase (5 U/µl) and 2 µl of PCR primers (each 100 pmoles) were added to the above 20 µl of the reverse transcription reaction solutions; 80 µl portions of the mineral oil were overlaid thereon; and PCR reactions were successingly performed. Each reaction was performed by 30 repeating 30 times the cycle of 94°C for 1.5 minutes, 50°C for 2 minutes and then 72°C for 3 minutes. The base sequences of the PCR primers are shown below. The primers contained in a Ig-Prime™ kit (produced by Novagen Co.) were used except for the primer of the leader sequence C for H chains.

35 Primer for H chains	
Leader sequence A	5' GGGATTACATGRASTTSKGGYTMARCTKGRTTT 3'
Leader sequence B	5' GGGATTACATGRAATGSASCTGGGYWTYCTCTT 3'
Leader sequence C	5' TTAAATGGTATCCAGTG 3'
Constant region	5' CCCAAGCTTCCAGGGRCCARKGGATARACIGRTGG 3'

45 Primer for L chains	
Leader sequence A	5' GGGATTACATGRAGWCACAKWCYCAGGTCTTT 3'
Leader sequence B	5' GGGATTACATGGAGACAGACACACTCCTGCTAT 3'
Constant region	5' CCCAAGCTTACTGGATGGTGGGAAGATGGA 3'

55 In the above, the alphabets other than A, G, C and T mean the following bases. R=A/G, W=A/T, I=inosine, Y=C/T, D=A/G/T, K=G/T, H=A/C/T, S=C/G, V=A/C/G, M=A/C, B=G/C/T

10 µl portions of the resultant 100 µl each of the PCR reaction products are subjected to 1.5% agarose gel electrophoresis, and it was confirmed that the antibody gene fragments each about 600 bp long were amplified. As a result, in the case of the H chains, the antibody genes derived from No. 3 and No. 17 were amplified in the leader sequence A,

the antibody genes derived from No. 20 and No. 27 were amplified in the leader sequence B, and the antibody gene derived from No. 33 was amplified in the leader sequence C. On the other hand, in the L chains, the antibody genes derived from No. 27 and No. 33 were amplified in the case where the leader sequence A was used, and the antibody genes derived from No. 3, No. 17 and No. 20 were amplified in the leader sequence B.

5 Each of the PCR-amplified fragments about 600 bp long was integrated into pCR 1000 vector or pCR™ vector using TA cloning kit (produced by Invitrogen Co.). Specifically, ligation mix solutions were prepared by mixing 1 μ l portions of the PCR reaction products, 1 μ l portions of 10 x the ligation buffer, 2 μ l portions of pCR1000 or pCR™ vector (corresponding to 50 μ g), 1 μ l of T4 DNA ligase and 6 μ l portions of sterilized water, respectively; and incubated overnight at 12°C. Separately, 50 μ l portions of a suspension of a competent *Escherichia coli* INVαT strain, to which portions were 10 added 2 μ l portions of 0.5 M β -mercaptoethanol, respectively, were prepared; and 1 μ l portions of the above ligation mix solutions are added thereto, respectively. The mixtures are allowed to stand on ice for 30 minutes, incubated at 42°C for one minute, and rapidly cooled on ice for 2 minutes. 450 μ l portions of SOC medium warmed to 42°C in advance were added to the resultant *Escherichia coli* solutions, respectively, and the mixtures are cultured with shaking at 37°C for one hour. Meanwhile, 25 μ l portions of X-Gal (40 mg/ μ l) are spreaded onto a number of LB agar plates each containing 15 Kanamycin (50 μ g/ml), respectively, and the agar plates are incubated at 37°C until each X-Gal completely permeates the agar plate.

200 μ l portions of the *Escherichia coli* culture broths after completion of culture were spread on the agar plate dried, respectively, and the plates were allowed to stand at 37°C overnight to give white colonies each having Kanamycin resistance.

20 Plasmids were purified from the *Escherichia coli* clones containing the respective antibody genes, and named 3KB11, 17KB1, 20KB1, 27KA2, 33KA26, 3GB1, 17GB7, 20GA2, 27GA5 and 33GC003, respectively. Purification of the plasmids is performed as follows.

The *Escherichia coli* strains containing the above plasmids, respectively, are cultured 37°C overnight in 100 ml portions of LB medium containing Kanamycin (50 μ g/ml), respectively. Each of the resultant culture broths is centrifuged 25 at 3,000 rpm for 10 minutes; the cells collected are suspended in 3 ml of an ice-cooled suspension (50 mM glucose, 10 mM EDTA, 2 mM Tris-HCl pH 8.0); and the suspension is allowed to stand at room temperature for 5 minutes. 6 ml of an alkali lysing solution (0.2 N sodium hydroxide, 1% SDS) is added, and the mixture is mixed by gently turning the centrifugation vessel upside down, and allowed to stand on ice for 5 minutes. 4.5 ml of an ice-cooled neutralizing solution (5 M potassium acetate pH 4.8) is added, and the mixture is centrifuged at 12,000 rpm and 4°C for 10 minutes. The 30 supernatant is transferred into another centrifugation vessel; 1 ml of heat-treated 100 μ g/ml RNase A solution is added; and the mixture is subjected to reaction for one hour in an incubator of 37°C to perform RNA digestion. To the reaction solution are added 6 ml of TE buffer-saturated phenol and 6 ml of chloroform/isoamyl alcohol (24:1), and the mixture is subjected to vortex for 30 seconds and then centrifuged at 10,000 rpm and 4°C for 3 minutes. The aqueous layer is transferred into another centrifugation vessel, an equal amount of isopropanol is added, and the mixture is sufficiently 35 mixed and then centrifuged at 10,000 rpm and room temperature for 10 minutes.

The resultant precipitate is washed with 1 ml of 70% cold (-20°C) ethanol, dried under reduced pressure, and dissolved in 480 μ l of sterilized water. The solution is transferred into an Eppendorf tube; 120 μ l of 4 M NaCl and 600 μ l of 40 13% polyethylene glycol #6000 are added; and the mixture is allowed to stand on ice for 20 minutes. The mixture is then centrifuged at 10,000 rpm and 4°C for 10 minutes, and the precipitate is washed with 1 ml of 70% cold (-20°C) ethanol, dried under reduced pressure and dissolved in 100 μ l of TE buffer. The resultant purified plasmid was used as a template for sequencing reaction.

Example 6: Determination of the base sequences

45 Sanger reactions were performed using as templates the plasmids cloning purified in Example 5 and a fluorescence-labeled primer; the reaction products were analyzed by a DNA sequencer DSQ-1 (produced by Shimadzu Corporation); and the DNA base sequences of the insert parts of the plasmids were also determined.

The sequencing reactions were performed using AmpliTaq cycle sequencing kit (produced by Takara Shuzo Co., Ltd.) and a fluorescence-labeled primer in a reagent kit (produced by Wakunaga Pharmaceutical Co., Ltd.) exclusively 50 used for a fluorescence-type DNA sequencer. First, 2 to 4 μ g of one of the plasmids purified as stated in Example 5 is mixed with 1 μ l of the FITC-labeled primer (1 p mole/ μ l, forward or reverse is used) and 2 μ l of the 10 x cycling mix solution, and sterilized water is added to prepare 10 μ l in final volume of a reaction mix. Four tubes are prepared in which 2 μ l portions of the termination mix (A, G, C, T) were placed in advance, respectively. 2 μ l portions of the above reaction mix were taken and placed into the respective tubes. The mixtures are corrected by centrifugation, 10 μ l portions 55 of a mineral oil are overlaid, and cycling reactions are performed under the following conditions; Precycle 95°C, 3 minutes; first cycle 95°C 30 seconds, 60°C 30 seconds, 72°C 1 minute (repeated 15 times); second cycle 95°C 30 seconds, 72°C 1 minute (repeated 15 times); postcycle 4°C.

2 μ l portions of a reaction-stopping dye solution (95% formaldehyde, 20 mM EDTA, 0.05% methyl violet) are added, and the mixtures are mixed by centrifugation and preserved at 20°C until they are electrophoresed.

As 5% polyacrylamide gel was used one obtained by adding pure water to 30 g of urea, 6 ml of 10 x TBE buffer (0.89 M Tris-HCl, 0.89 M boric acid, 0.025 M EDTA disodium salt) and 10 ml of 30% acrylamide solution (28.5% acrylamide and 1.5% methylenebisacrylamide, both produced by BIO-RAD Co.) to make the whole volume 60 ml; filtering the mixture with 0.22-μm filter; deaerating the filtrate for 30 minutes; adding 150 μl of 10% ammonium persulfate and 15 μl of TEMEO; allowing the mixture to stand overnight to make it gel.

The gel was set in the DNA sequencer DSQ-1, and prerun was performed at a constant voltage of 1,000 V for one hour. Each of the samples was denatured at 95°C for 3 minutes immediately before electrophoresis, and rapidly cooled on ice, and 2 to 3 μl of the reaction solution was sucked up from the bottom part of the tube by a micro-syringe and loaded onto the gel. Samples run was performed at a constant electric power of 20 W for 12 hours.

After completion of electrophoresis, the base sequence was determined using the software attached to DSO-1. The sequence was confirmed by sequencing both of the sense and antisense chains of the same plasmid from both directions.

The resultant base sequences of the variable regions of the H chains and L chains of the five kinds of the mouse monoclonal antibodies, and amino acid sequences presumed therefrom are shown in the following sequence listing. Relation between the sequence numbers and the sequences of the clones are as follows:

Sequence No. 1 : Idio 3 H chain variable region (clone 3GB1)
 Sequence No. 2 : Idio 17 H chain variable region (clone 17GB7)
 Sequence No. 3 : Idio 20 H chain variable region (clone 20GA2)
 Sequence No. 4 : Idio 27 H chain variable region (clone 27GA5)
 Sequence No. 5 : Idio 33 H chain variable region (clone 33GC003)
 Sequence No. 6 : Idio 3 L chain variable region (clone 3KB11)
 Sequence No. 7 : Idio 17 L chain variable region (clone 17KB1)
 Sequence No. 8 : Idio 20 L chain variable region (clone 20KB1)
 Sequence No. 9 : Idio 27 L chain variable region (clone 27KA2)
 Sequence No. 10 : Idio 33 L chain variable region (clone 33KA26)

Example 7 Determination of hypervariable regions

The amino acid sequences obtained in Example 6 were notated in parallel according to the numbering of Kabat et al.'s data base (Sequences of proteins of immunological interest Fifth edition, U. S. Department of health and human services. Public health service, National Institutes of Health. NIH Publication No. 91-3242, Kabat et al. 1991), and the amino acid sequences of the hypervariable regions CDR1, CDR2 and CDR3 of each antibody were identified (Fig. 4, H chains, Fig. 5 L chains). In order to confirm the novelty of the identified amino acid sequences of the hypervariable regions CDR1, CDR2 and CDR3, retrieval by a computer was performed using the above Kabat et al.'s data base and a protein data base NBRF-PDB (National Biomedical Research Foundation - protein data base) Release 36.

As a result, the amino acid sequences of Idio 3 H chain CDR1, Idio 17 H chain CDR1, Idio 20 H chain CDR1, Idio 27 H chain CDR1, Idio 33 H chain CDR2, Idio 3 L chain CDR2, Idio 17 L chain CDR2, Idio 27 L chain CDR2 and Idio 33 L chain CDR2 were the same as those of known antibodies, but the amino acid sequences of other CDRs were

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revealed to be novel sequences.

Sequence Listing

5 Seq. I.D. number : 1

Sequence length : 399

Sequence type : nucleic acid

10 Strandedness : double

Topology : linear

Sequence kind : mRNA

Original source

Organism : mouse

15 Sequence characteristics

Symbol expressing characteristics : CDS

Presence position : 1..399

20 Characteristics determination method : S

Symbol expressing characteristics : sig peptide

Presence position : 1..27

Characteristics determination method : S

25 Sequence

CTG TCG GTA ACT TCA GGG GTC TAC TCA GAG GTT CAG CTC CAG CAG TCT 48

Leu Ser Val Thr Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser

-5 1 5

GGG ACT GTG CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG TCC TGC AAG 96

30 Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys

10 15 20

GCT TCG GGC TAC ACC TTT AAC AGC TAC TGG ATG CAC TGG GTA AAA CAG 144

Ala Ser Gly Tyr Thr Phe Asn Ser Tyr Trp Met His Trp Val Lys Gln

25 30 35

35 AGG CCT GGA CAG GGT CTG GAA TGG ATT GGC GCG ATT TAT CCT GGA AAT 192

Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn

40 45 50 55

AGT GAT ATT AGC TAC AGC CAG AAC TTT AAG GAC AGG GCC AAA CTG ACT 240

40 Ser Asp Ile Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu Thr

60 65 70

60 GCC GTC ACA TCC ACC AGC ACT GCC TAC ATG GAA CTC AGA AGC CTG ACA 288

Ala Val Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr

75 80 85

45 AAT GAG GAC TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA TAT GAT TAC 336

Asn Glu Asp Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu Tyr Asp Tyr

90 95 100

50 GAC ACC CTG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC TCA 384

Asp Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser

105 110 115

50 GCC AAA ACG ACA CCC 399

Ala Lys Thr Thr Pro

120

Sequence Listing

Seq. I.D. number : 2
Sequence length : 402
Sequence type : nucleic acid
Strandedness : double
Topology : linear
Sequence kind : mRNA
Original source

Sequence characteristics

Symbol expressing characteristics : CDS

Presence position : 1..402

Characteristics determination method : S

Symbol expressing characteristics : sig peptide

Presence position : 1..30

Characteristics determination method : S

Sequence

ATT CTG TCG GTA ACT TCA GGG GTC TAC TCA GAG GTT CAG CTC CAG CAG
Ile Leu Ser Val Thr Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln
-10 -5 1 5

TCT GGG ACT GTG CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG TCC TGC
Ser Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys

10	15	20
AAG GCT TCG GGC TAC ACC TTT AAC AGC TAC TGG ATG CAC TGG GTA AAA		
Lys Ala Ser Gly Tyr Thr Phe Asn Ser Tyr Trp Met His Trp Val Lys		

25	30	35
CAG AGG CCT GGA CAG GGT CTG GAA TGG ATT GGC GGG ATT TAT CCT GGA		
Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Glv Ala Ile Tyr Pro Gly		

40 45 50
AAT AGT GAT ATT AGC TAC AGC CAG AAC TTT AAG GAC AGG GCC AAA CTG
Asn Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu

ACT GCC GTC ACA TCC ACC AGC ACT GCC TAC ATG GAA CTC AGA AGC AGC CTG
The Ala Val The Ser The Ser The Ala Phe Met Glu

Asn Glu Asp Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu Tyr Asp
 90 95 100
 TAC GAC ACC CTG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC

Tyr Asp Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
 105 110 115
 CA GCC AAA ACG ACA CCC

Ser Ala Lys Thr Thr Pro
120

120

55

Sequence Listing

Sequence Listing

Seq. I.D. number : 4

Sequence length : 411

Sequence type : nucleic acid

Strandedness : double

Topology : linear

Sequence kind : mRNA

Original source

Organism : mouse

Sequence characteristics

Symbol expressing characteristics : CDS

Presence position : 1..411

Characteristics determination method : S

Symbol expressing characteristics : sig peptide

Presence position : 1..30

Characteristics determination method : S

Sequence

25	CTT GTA ACA CGT TTA AAT GGT ATC CAG TGT GAG GTG AAG CTG GTG GAG	48
	Leu Val Thr Arg Leu Asn Gly Ile Gln Cys Glu Val Lys Leu Val Glu	
	10 -5 . 1 5	
	TCT GGA GGA GGC TTG GTA CAG CCT GGG GGT TCT CTG AGA CTC TCC TGT	96
	Ser Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys	
30	10 15 20	
	GCA ACT TCT GGG TTC ACC TTC ACT GAT TAC TAC ATG AAC TGG GTC CGC	144
	Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Arg	
	25 30 35	
35	CAG CCT CCA GGA AAG GCA CTT GAG TGG TTG GGT TTT ATT AGA AAC AAA	192
	Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys	
	40 45 50	
	GCT AAT TAT TAC ACA ACA GAG TAC AGT GCA TCT GTG AAG GGT CGG TTC	240
	Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe	
40	55 60 65	
	ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC CTC TAT CTT CAA ATG AAC	288
	Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn	
	70 75 80 85	
45	ACC CTG AGA GCT GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA GAT GGG	336
	Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Gly	
	90 95 100	
	TTC CTA CGG GAC TGG TAC TTC GAT GTC TGG GGC GCA GGG ACC ACG GTC	384
	Phe Leu Arg Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val	
50	105 110 115	
	ACC GTC TCC TCA GCC AAA ACG ACA CCC	411
	Thr Val Ser Ser Ala Lys Thr Thr Pro	
	120 125	

Sequence Listing

5 Seq. I.D. number : 5
 Sequence length : 363
 Sequence type : nucleic acid
 10 Strandedness : double
 Topology : linear
 Sequence kind : mRNA
 Original source

15 Organism : mouse

Sequence characteristics

Symbol expressing characteristics : CDS
 20 Presence position : 1..363
 Characteristics determination method : S

Sequence

25	GAG GTT CAG CTC CAG CAG TCT GGG GCT GAA CTG GCA AGA CCT GGG GCT	48
	Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala	
	1 5 10 15	
	TCA GTG AAC TTG TCC TGC AAG GCT TCT GGC TAC ACC TTT ACT AAC TAC	96
	Ser Val Asn Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr	
30	20 25 30	
	TGG ATG CAG TGG GTA AAA CAG AGG CGT GGA CAG GGT CTG GAA TGG ATT	144
	Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile	
	35 40 45	
35	GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGG TAC ACT CAG AAG TTC	192
	Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe	
	50 55 60	
40	AAG GGC AAG GCC ACA TTG ACT GCA GCT AAA TCC TCC AGC ACA GCC TAC	240
	Lys Gly Lys Ala Thr Leu Thr Ala Ala Lys Ser Ser Ser Thr Ala Tyr	
	65 70 75	
	ATG CAA CTC AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT	288
	Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys	
45	80 85 90 95	
	GCA AGA TCG GGC TAC TAT GGT AGC TTC GTT GGG TTT GCT TAC TGG GGC	336
	Ala Arg Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Phe Ala Tyr Trp Gly	
	100 105 110	
50	CAA GGG ACT CTG GTC ACT GTC TCT GCA	363
	Gln Gly Thr Leu Val Thr Val Ser Ala	
	115 120	

Sequence Listing

5 Seq. I.D. number : 6

Sequence length : 354

Sequence type : nucleic acid

10 Strandedness : double

Topology : linear

Sequence kind : mRNA

Original source

15 Organism : mouse

Sequence characteristics

Symbol expressing characteristics : CDS

20 Presence position : 1..354

Characteristics determination method : S

Sequence

GAC ATT GTG CTG ACA CAG TCT CCT GCT TCA GCT GTA TCT CCT CTG	48
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Leu	
1 5 10 15	
GGG CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC AAA AGT GTG CAG TTA	96
Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Gln Leu	
20 25 30	
CAT CTG GCT ATA GTT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG	144
His Leu Ala Ile Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln	
35 40 45	
CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC	192
Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val	
50 55 60	
CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC	240
Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn	
65 70 75	
ATC CAT CCT GTG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC	288
Ile His Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His	
80 85 90 95	
ATT AGG GTA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA	336
Ile Arg Val Ala Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys	
100 105 110	
CGG GCT GAT GCT GCA CCA	354
Arg Ala Asp Ala Ala Pro	
115	

Sequence Listing

Sequence Listing

Seq. I.D. number : 8

Sequence length : 417

Sequence type : nucleic acid

Strandedness : double

Topology : linear

Sequence kind : mRNA

Original source

Organism : mouse

Sequence characteristics

Symbol expressing characteristics : CDS

Presence position : 28..417

Characteristics determination method : S

Symbol expressing characteristics : sig peptide

Presence position : 28..90

Characteristics determination method : S

Sequence

GGCCGCG GTGAGAACCG TTGGGAATTC ATG GAG ACA GAC ACA CTC CTG 48

Met Glu Thr Asp Thr Leu Leu

-20 -15

CTA TGG GTA CTG CTG CTC TGG GTT CCA GGT TCC ACT GGT GAC ATT GTG 96

Leu Trp Val Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Val

-10 -5 1

CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG CGG CAG AGG GCC 144

Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala

5 10 15

ACC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT GGC TAT AGT 192

Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser

20 25 30

TAT ATG CAC TGG AAC CAA CAG AGA CCA GGA CAG CCA CCC AGA CTC CTC 240

Tyr Met His Trp Asn Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu

40 35 40 45 50

ATC TAT CTT GTA TCC AAC CTA GAC TCT GGG GTC CCT GCC AGG TTC AGT 288

Ile Tyr Leu Val Ser Asn Leu Asp Ser Gly Val Pro Ala Arg Phe Ser

55 60 65

GGC ACT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT CCT GTG GAG 336

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu

70 75 80

GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT GAG GGA GCT TAC 384

Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Glu Gly Ala Tyr

85 90 95

50 ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 417

Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys

100 105

Sequence Listing

5 Seq. I.D. number : 9
 Sequence length : 420
 Sequence type : nucleic acid
 Strandedness : double
 10 Topology : linear
 Sequence kind : mRNA
 Original source
 Organism : mouse

15 Sequence characteristics
 Symbol expressing characteristics : CDS
 Presence position : 31..420
 Characteristics determination method : S

20 Symbol expressing characteristics : sig peptide
 Presence position : 31..90
 Characteristics determination method : S

Sequence

25	GC GG CC CG CG TG AGA ACC GT TT GGG AATT TC AT G GAG A CA C AG T CC C AG	48	
	Met Glu Thr Gln Ser Gln		
	-20	-15	
30	GTC TTT GTA TTC GTG TTT CTC TGG TTG TCT GGT GTT GAC GGA GAC ATT Val Phe Val Phe Val Phe Leu Trp Leu Ser Gly Val Asp Gly Asp Ile	96	
	-10	-5	1
	GTG ATG ACC CAG TCT CAC AAA TTC ATG TCC ACA TCA GTA GGA GAC AGG	144	
	Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg		
	5 10 15		
35	GTC AGT ATC ACC TGC AAG GCC AGT CAG GAT GTG AAT ACT GCT GTA GCC	192	
	Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala		
	20 25 30		
	TGG TAT CAA CAG AAA CCA GGA CAA TCT CCT AAA CTA CTG CTT TAC TCG	240	
	Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Leu Tyr Ser		
40	35 40 45		
	GCA TCC TAC CGG TAC ACT GGA GTC CCT GAT CAC TTC ACT GGC AGT GGA	288	
	Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp His Phe Thr Gly Ser Gly		
	50 55 60 65		
	TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC GGT GTG CAG GCT GAA GAC	336	
45	Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Val Gln Ala Glu Asp		
	70 75 80		
	CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT CCT CCT CTC ACG TTC	384	
	Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Leu Thr Phe		
	85 90 95		
50	GGT GCT GGG ACC AAG CTG GAA CTG AAA CGG GCT GAT	420	
	Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp		
	100 105		

Sequence Listing

5 Seq. I.D. number : 10
 Sequence length : 360
 Sequence type : nucleic acid
 Strandedness : double
 10 Topology : linear
 Sequence kind : mRNA
 Original source
 15 Organism : mouse

Sequence characteristics

Symbol expressing characteristics : CDS
 Presence position : 1..360
 20 Characteristics determination method : S
 Symbol expressing characteristics : sig peptide
 Presence position : 1..12
 Characteristics determination method : S

Sequence

GGT GTT GAC GGA GAC ATT GTG ATG ACA CAG TCT CAC AAA TTC ATG TCC	48
Gly Val Asp Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser	
1 5 10	
ACA TCA GTT GGA GAC AGG GTC ACC ATC ACC TGC AAG GCC AGT CAG GAT	96
Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp	
15 20 25	
GTG ACT ACT GAT GTA GCC TGG TAT CAA CAG AAA CCA CGA CAA TCT CCT	144
Val Thr Thr Asp Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro	
30 35 40	
AAA CTA CTG ATT TAC TCG GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT	192
Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp	
45 50 55	
CGC TTC ACT GGC AGT GGA TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC	240
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser	
60 65 70 75	
AGT GTG CAG GCT GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT	288
Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr	
80 85 90	
AGT ACT GCG TCG ACG TTC GGT GGT GGC ACC AAG CTG GAA ATC AAA CGG	336
Ser Thr Ala Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg	
95 100 105	
GCT GAT GCT GCA CCA ACT GTA TCC	360
Ala Asp Ala Ala Pro Thr Val Ser	
110 115	

SEQUENCE LISTING

5

(1) GENERAL INFORMATION:

(i) APPLICANT:

10

- (A) NAME:HAGIWARA, Yoshihide
- (B) STREET:4-14, Hiraisanso
- (C) CITY:Takarazuka-shi
- (D) STATE:Hyogo-ken
- (E) COUNTRY:Japan
- (F) POSTAL CODE (ZIP):none

15

(ii) TITLE OF INVENTION:AMINO ACID SEQUENCES OF ANTI-IDIOTYPIC ANTIBODIES AGAINST ANTI-CANCER HUMAN MONOCLONAL ANTIBODY, AND DNA BASE SEQUENCES ENCODING THOSE SEQUENCES

20

(iii) NUMBER OF SEQUENCES:48

25

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE:Floppy disk
- (B) COMPUTER:IBM PC compatible
- (C) OPERATING SYSTEM:MS DOS 4.0
- (D) SOFTWARE:Microsoft Word, Version 5.5

30

(v) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER:EP 94 115 683.8
- (B) FILING DATE:October 5, 1994

35

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:5 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:H-CDR1-1
- (D) OTHER INFORMATION:hypervariable region

40

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:1:

Ser Tyr Trp Met His

5

45

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:5 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

50

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:H-CDR1-2
- (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 2:

55

Asp Tyr Tyr Met Asn

5

5

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:5 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

10

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:H-CDR1-3
- (D) OTHER INFORMATION:hypervariable region

15

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:3:

Asn Tyr Trp Met Gln

5

20

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:17 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

25

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:H-CDR2-1
- (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 4:

30

Ala Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys

5

10

15

Asp

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:19 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

40

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:H-CDR2-2
- (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:5:

45

Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr Asp Tyr Ser Ala Ser

5

10

15

Val Lys Gly

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:19 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

50

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

55

(A) NAME/KEY:H-CDR2-3
 (D) OTHER INFORMATION:hypervariable region

5

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 6:

Phe Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser
 5 10 15
 Val Lys Gly

10

(2) INFORMATION FOR SEQ ID NO: 7:

15

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:17 amino acids

(B) TYPE:amino acid
 (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:H-CDR2-4
 (D) OTHER INFORMATION:hypervariable region

20

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:7:

Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Glu Lys Phe Lys
 5 10 15
 Gly

25

(2) INFORMATION FOR SEQ ID NO: 8:

30

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:10 amino acids

(B) TYPE:amino acid
 (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:H-CDR3-1
 (D) OTHER INFORMATION:hypervariable region

35

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 8:

Glu Glu Tyr Asp Tyr Asp Thr Leu Asp Tyr
 5 10

40

(2) INFORMATION FOR SEQ ID NO: 9:

45

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:11 amino acids

(B) TYPE:amino acid
 (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:H-CDR3-2
 (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:9:

50

Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp Val
 5 10

55

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:11 amino acids

(B) TYPE:amino acid

(D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:H-CDR3-3

(D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 10:

Asp Gly Phe Leu Arg Asp Trp Tyr Phe Asp Val
5 10

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:12 amino acids

(B) TYPE:amino acid

(D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:H-CDR3-4

(D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:11:

Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr
5 10

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:17 amino acids

(B) TYPE:amino acid

(D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:L-CDR1-1

(D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 12:

Tyr Arg Ala Ser Lys Ser Val Gln Leu His Leu Ala Ile Val Tyr Met
5 10 15
His

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:16 amino acids

(B) TYPE:amino acid

(D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

(A) NAME/KEY:L-CDR1-2

(D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:13:

Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His
5 10 15

(2) INFORMATION FOR SEQ ID NO: 14:

5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:11 amino acids
 (B) TYPE:amino acid
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:protein
 (ix) FEATURE:
 (A) NAME/KEY:L-CDR1-3
 (D) OTHER INFORMATION:hypervariable region
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 14:

15 Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala
 5 10

(2) INFORMATION FOR SEQ ID NO: 15:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:11 amino acids
 (B) TYPE:amino acid
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:protein
 (ix) FEATURE:
 (A) NAME/KEY:L-CDR1-4
 (D) OTHER INFORMATION:hypervariable region
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:15:

25 Lys Ala Ser Gln Asp Val Thr Thr Asp Val Ala
 5 10

30 (2) INFORMATION FOR SEQ ID NO: 16:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:7 amino acids
 (B) TYPE:amino acid
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:protein
 (ix) FEATURE:
 (A) NAME/KEY:L-CDR2-1
 (D) OTHER INFORMATION:hypervariable region
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 16:

40 Leu Val Ser Asn Leu Glu Ser
 5

45 (2) INFORMATION FOR SEQ ID NO: 17:

50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:7 amino acids
 (B) TYPE:amino acid
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:protein
 (ix) FEATURE:
 (A) NAME/KEY:L-CDR2-2
 (D) OTHER INFORMATION:hypervariable region
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:17:

Leu Val Ser Asn Leu Asp Ser

5

(2) INFORMATION FOR SEQ ID NO: 18:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH:7 amino acids
 - (B) TYPE:amino acid
 - (D) TOPOLOGY:linear
- (ii) MOLECULE TYPE:protein
- (ix) FEATURE:
 - (A) NAME/KEY:L-CDR2-3
 - (D) OTHER INFORMATION:hypervariable region
- (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 18:

Ser Ala Ser Tyr Arg Tyr Thr

5

(2) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH:8 amino acids
 - (B) TYPE:amino acid
 - (D) TOPOLOGY:linear
- (ii) MOLECULE TYPE:protein
- (ix) FEATURE:
 - (A) NAME/KEY:L-CDR3-1
 - (D) OTHER INFORMATION:hypervariable region
- (xi) SEQUENCE DESCRIPTION:SEQ ID NO:19:

Gln His Ile Arg Val Ala Tyr Thr

5

(2) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH:8 amino acids
 - (B) TYPE:amino acid
 - (D) TOPOLOGY:linear
- (ii) MOLECULE TYPE:protein
- (ix) FEATURE:
 - (A) NAME/KEY:L-CDR3-2
 - (D) OTHER INFORMATION:hypervariable region
- (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 20:

Gln His Ile Arg Gly Ala Tyr Thr

5

(2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH:8 amino acids
 - (B) TYPE:amino acid
 - (D) TOPOLOGY:linear
- (ii) MOLECULE TYPE:protein
- (ix) FEATURE:
 - (A) NAME/KEY:L-CDR3-3
 - (D) OTHER INFORMATION:hypervariable region

55

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:21:

5 Gln His Ile Glu Gly Ala Tyr Thr
5

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:9 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:L-CDR3-4
- (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 22:

Gln Gln His Tyr Ser Pro Pro Leu Thr
5

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:9 amino acids
- (B) TYPE:amino acid
- (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:protein

(ix) FEATURE:

- (A) NAME/KEY:L-CDR3-5
- (D) OTHER INFORMATION:hypervariable region

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:23:

Gln Gln His Tyr Ser Thr Ala Trp Thr
5

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:34 base pairs
- (B) TYPE:nucleic acid
- (C) STRANDEDNESS:single
- (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:cDNA

(iv) ANTISENSE:no

(iii) HYPOTHETICAL:no

(ix) FEATURE:

- (A) NAME/KEY:H Leader Sequence A
- (D) OTHER INFORMATION:R is A or G;

S is C or G;

K is G or T;

Y is C or T;

M is A or C.

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 24:

50 GGGAAATTCAT GRASSTTSKGG YYTMRARCTKG RTTT

34

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

55

5 (A) LENGTH:34 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:cDNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (ix) FEATURE:
 10 (A) NAME/KEY:H Leader Sequence B
 (D) OTHER INFORMATION:S is C or G;
 Y is C or T;
 W is A or T;
 R is A or G.
 15 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:25:

GGGAATTCCAT GRAATGSASC TGGGTYWTYC TCTT

34

(2) INFORMATION FOR SEQ ID NO: 26:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:18 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:cDNA
 25 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (ix) FEATURE:
 (A) NAME/KEY:H Leader Sequence C
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 26:

30 TTAAATGGTA TCCAGTGT

18

(2) INFORMATION FOR SEQ ID NO: 27:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:35 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:cDNA
 (iii) HYPOTHETICAL:no
 40 (iv) ANTISENSE:no
 (ix) FEATURE:
 (A) NAME/KEY:H Constant Region
 (D) OTHER INFORMATION:R is A or G;
 K is G or T;
 N is inosine.
 45 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:27:

CCCCAAGCTTC CAGGGRCCAR KGGATARACN GRTGG

35

(2) INFORMATION FOR SEQ ID NO: 28:

50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:32 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear

GGGAATTCA GRAGWCACAK WCYCAGGTCT TT

32

15 (2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:33 base pairs

(B) TYPE:nucleic acid

(C) STRANDEDNESS:single

(D) TOPOLOGY:linear

20 (ii) MOLECULE TYPE:cDNA

(iii) HYPOTHETICAL:no

(iv) ANTISENSE:no

(ix) FEATURE:

(A) NAME/KEY:L Leader Seq

25 (xi) SEQUENCE DESCRIPTION:SEQ ID

GGAATTCAAT GGAGACAGAC AACTCCTGC TAT

33

30 (2) INFORMATION FOR SEQ ID NO: 30:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:30 base pairs
- (B) TYPE:nucleic acid
- (C) STRANDEDNESS:single
- (D) TOPOLOGY:linear

35 (ii) MOLECULE TYPE:cDNA

(iii) HYPOTHETICAL:no

(iv) ANTISENSE:no

(ix) FEATURE:

- (A) NAME/KEY:L constant

40 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 30:

CCCAAGCTTA CTGGATGGTG GGAAGATGGA

30

(2) INFORMATION FOR SEQ ID NO: 31:

45 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:357 base pairs
(B) TYPE:nucleic acid
(C) STRANDEDNESS:double
(D) TOPOLOGY:linear

50 (ii) MOLECULE TYPE:mRNA
(iii) HYPOTHETICAL:no
(iv) ANTISENSE:no
(vi) ORIGINAL SOURCE:
(A) ORGANISM:mouse
(ix) FEATURE:

(xi) (A) NAME/KEY: Idio 3 H chain variable/Idio 17 H chain variable
SEQUENCE DESCRIPTION: SEQ ID NO: 31:

GAG GTT CAG CTC GAG CAG TCT GGG ACT GTG CTG GCA AGG CCT GGG GCT 48
 Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
 5 10 15

10 TCA GTG AAG ATG TCC TGC AAG GCT TCG GGC TAC ACC TTT AAC AGC TAC 96
 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn Ser Tyr
 20 25 30

TGG ATG CAC TGG GTA AAA CAG AGG CCT GGA CAG GGT CTG GAA TGG ATT 144
 Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

```

GGC GCG ATT TAT CCT GGA AAT AGT GAT ATT AGC TAC AGC CAG AAC TTT 192
Gly Ala Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr Ser Gln Asn Phe
      50          55          60

```

20 AAG GAC AGG GCC AAA CTG ACT GCC GTC ACA TCC ACC AGC ACT GCC TAC 240
 Lys Asp Arg Ala Lys Leu Thr Ala Val Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

ATG GAA CTC AGA AGC CTG ACA AAT GAG GAC TCT GCG GTC TAT TTC TGT 288
 Met Glu Leu Arg Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Phe Cys
 25 85 90 95

ACA	AAA	GAG	GAA	TAT	GAT	TAC	GAC	ACC	CTG	GAC	TAC	TGG	GGT	CAA	GGA	336
Thr	Lys	Glu	Glu	Tyr	Asp	Tyr	Asp	Thr	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	
		100				105							110			

30 ACC TCA GTC ACC GTC TCC TCA
Thr Ser Val Thr Val Ser Ser
115

(2) INFORMATION FOR SEQ ID NO: 32:

35 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 366 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: mRNA

(iii) HYPOTHETICAL: no

(iv) ANTISENSE: no

(vi) ORIGINAL SOURCE

(A) ORGANISM: mouse

(ix) FEATURE:

(A) N

(x1) SEQUENCE DESCRIPTION:SEQ ID NO: 32:

GAG CTG AAC CTG CTG GAG TCT GCG GCG GCG TTT

GAG GTC AAG CTC GAG TCT GGA GGA GGC TTG GTA CAG CCT GGG GGT 48
 Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 10 15

TCT CTC AGA CTC TCC TGT GCA ACT TCT GGG TTA ACC TTC ACT GAT TAC 96
 Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr Phe Thr Asp Tyr
 20 25 30

TAC ATG AAC TGG GTC CGC CAG CCT CCA GGA AAG GAA CTT GAA TGG TTG 144
 Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Glu Leu Glu Trp Leu
 35 40 45

5

GGT TTT ATT AGA AAC AAA GCT AAT CTT TAC ACA ACA GAC TAC AGT GCA 192
 Gly Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr Asp Tyr Ser Ala
 50 55 60

10

TCT GTG AAG GGT CGG TTC ACC ATC TCC AGA CAT AAT CCC CAA AGC ATC 240
 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Gln Ser Ile
 65 70 75 80

15

CTC TAT CTT CAA ATG AAC ACC CTG ACA ACT GAG GAC AGT GCC ACT TAT 288
 Leu Tyr Leu Gln Met Asn Thr Leu Thr Thr Glu Asp Ser Ala Thr Tyr
 85 90 95

TAC TGT GCA AGA GAT AGG GGG GGG AGG GAC TGG TAC TTC GAT GTC TGG 336
 Tyr Cys Ala Arg Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp Val Trp
 100 105 110

20

GGC GCA GGG ACC ACG GTC ACC GTC TCC TCA 366
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser
 115 120

25

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 366 base pairs

(B) TYPE:nucleic acid

(C) STRANDEDNESS:double

(D) TOPOLOGY:linear

(ii) MOLECULE TYPE:mRNA

(iii) HYPOTHETICAL:no

(iv) ANTISENSE:no

(v) ORIGINAL SOURCE:

(A) ORGANISM:mouse

(ix) FEATURE:

(A) NAME/KEY:Idio 27 H chain variable

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 33:

30

GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC TTG GTA CAG CCT GGG GGT 48
 Glu Val Lys Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 5 10 15

35

TCT CTG AGA CTC TCC TGT GCA ACT TCT GGG TTC ACC TTC ACT GAT TAC 96
 Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30

40

TAC ATG AAC TGG GTC CGC CAG CCT CCA GGA AAG GCA CTT GAG TGG TTG 144
 Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
 35 40 45

45

GGT TTT ATT AGA AAC AAA GCT AAT TAT TAC ACA ACA GAG TAC AGT GCA 192
 Gly Phe Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Glu Tyr Ser Ala
 50 55 60

50

TCT GTG AAG GGT CGG TTC ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC 240
 Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
 65 70 75 80

CTC TAT CTT CAA ATG AAC ACC CTG AGA GCT GAG GAC AGT GCC ACT TAT 288
 Leu Gln Met Asn Thr Leu Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr
 85 90 95

TAC	TGT	GCA	AGA	GAT	GGG	TTC	CTA	CGG	GAC	TGG	TAC	TTC	GAT	GTC	TGG	336
Tyr	Cys	Ala	Arg	Asp	Gly	Phe	Leu	Arg	Asp	Trp	Tyr	Phe	Asp	Val	Trp	
100								105					110			

GGC GCA GGG ACC ACG GTC ACC GTC TCC TCA
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser
 115 120

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 363 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: mRNA
(iii) HYPOTHETICAL: no
(iv) ANTISENSE: no
(vi) ORIGINAL SOURCE:
(A) ORGANISM: mouse

(ix) FEATURE:
(A) NAME/KEY: Idio 33 H chain variable

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

TCA GTG AAC TTG TCC TGC AAG GCT TCT GGC TAC ACC TTT ACT AAC TAC 96
 Ser Val Asn Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30

TGG ATG CAG TGG GTA AAA CAG AGG CCT GGA CAG GGT CTG GAA TGG ATT 144
 Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGG TAC ACT CAG AAG TTC 192
 Gly Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe
 50 55 60

AAG	GGC	AAG	GCC	ACA	TTG	ACT	GCA	GCT	AAA	TCC	TCC	AGC	ACA	GCC	TAC	240
Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Ala	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	
65					70				75					80		

```

ATG CAA CTC AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT 288
Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85          90          95

```

5 GCA AGA TCG GGC TAC TAT GGT AGC TTC GTT GGG TTT GCT TAC TGG GGC 336
 Ala Arg Ser Gly Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr Trp Gly
 100 105 110

10 CAA GGG ACT CTG GTC ACT GTC TCT GCA 363
 Gln Gly Thr Leu Val Thr Val Ser Ala
 115 120

10 (2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
 15 (A) LENGTH:336 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 20 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse
 (ix) FEATURE:
 (A) NAME/KEY:Idio 3 L chain variable
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 35:

25 GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CCT CTG 48
 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Leu
 5 10 15

30 GGG CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC AAA AGT GTG CAG TTA 96
 Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Gln Leu
 20 25 30

CAT CTG GCT ATA GTT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG 144
 His Leu Ala Ile Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln
 35 40 45

35 CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC 192
 Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val
 50 55 60

40 CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC 240
 Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn
 65 70 75 80

45 ATC CAT CCT GTG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC 288
 Ile His Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His
 85 90 95

ATT AGG GTA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 336
 Ile Arg Val Ala Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

50 (2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:330 base pairs

5 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse
 10 (ix) FEATURE:
 (A) NAME/KEY:Idio 17 L chain variable
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 36:

 GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG 48
 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 15 5 10 15

 CAG AGG GCC TCC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT 96
 Gln Arg Ala Ser Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30

 20 GGC TAT AGT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC 144
 Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45

 25 AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC CCT GCC 192
 Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala
 50 55 60

 30 AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT 240
 Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80

 CCT GTG GAG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT AGG 288
 Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg
 85 90 95

 35 GGA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 330
 Gly Ala Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

 (2) INFORMATION FOR SEQ ID NO: 37:
 40 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:330 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear
 45 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse
 50 (ix) FEATURE:
 (A) NAME/KEY:Idio 20 L chain variable
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 37:

	GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG	48
5	Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly	
	5 10 15	
	CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT	96
	Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser	
	20 25 30	
10	GGC TAT AGT TAT ATG CAC TGG AAC CAA CAG AGA CCA GGA CAG CCA CCC	144
	Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Arg Pro Gly Gln Pro Pro	
	35 40 45	
15	AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAC TCT GGG GTC CCT GCC	192
	Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Asp Ser Gly Val Pro Ala	
	50 55 60	
	AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT	240
	Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His	
	65 70 75 80	
20	CCT GTG GAG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT GAG	288
	Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Glu	
	85 90 95	
25	GGA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA	330
	Gly Ala Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys	
	100 105 110	

(2) INFORMATION FOR SEQ ID NO: 38:

30	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 321 base pairs	
	(B) TYPE:nucleic acid	
	(C) STRANDEDNESS:double	
	(D) TOPOLOGY:linear	
35	(ii) MOLECULE TYPE:mRNA	
	(iii) HYPOTHETICAL:no	
	(iv) ANTISENSE:no	
	(vi) ORIGINAL SOURCE:	
	(A) ORGANISM:mouse	
40	(ix) FEATURE:	
	(A) NAME/KEY:Idio 27 L chain variable	
	(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 38:	
	GAC ATT GTG ATG ACC CAG TCT CAC AAA TTC ATG TCC ACA TCA GTA GGA	48
	Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly	
	5 10 15	
45	GAC AGG GTC AGT ATC ACC TGC AAG GCC AGT CAG GAT GTG AAT ACT GCT	96
	Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala	
	20 25 30	
50	GTA GCC TGG TAT CAA CAG AAA CCA GGA CAA TCT CCT AAA CTA CTG CTT	144
	Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Leu	
	35 40 45	

TAC TCG GCA TCC TAC CGG TAC ACT GGA GTC CCT GAT CAC TTC ACT GGC 192
 Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp His Phe Thr Gly
 50 55 60

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AGT GGA TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC GGT GTG CAG GCT 240
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Val Gln Ala
65          70          75          80

```

10 GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT CCT CCT CTC 288
 Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Leu
 85 90 95

15 ACG TTC GGT GCT GGG ACC AAG CTG GAA CTG AAA 321
 Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 100 105

(2) INFORMATION FOR SEQ ID NO: 39:

20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 321 base pairs
(B) TYPE:nucleic acid
(C) STRANDEDNESS:double
(D) TOPOLOGY:linear

25 (ii) MOLECULE TYPE:mRNA
(iii) HYPOTHETICAL:no
(iv) ANTISENSE:nó
(vi) ORIGINAL SOURCE:
(A) ORGANISM:mouse
(ix) FEATURE:
(A) NAME/KEY:Idio 33 L chain variable
30 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 39:

35 GAC AGG GTC ACC ATC ACC TGC AAG GCC AGT CAG GAT GTG ACT ACT GAT 96
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Asp
 20 25 30

40 GTA GCC TGG TAT CAA CAG AAA CCA CGA CAA TCT CCT AAA CTA CTG ATT 144
 Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro Lys Leu Leu Ile
 35 40 45

TAC TCG GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT CGC TTC ACT GGC 192
 Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
 50 55 60

AGT GGA TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC AGT GTG CAG GCT 240
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
 65 70 75 80

50 GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT ACT GCG TGG 288
 Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Ala Trp
 85 90 95

321

5 ACG TTC GGT GGC ACC AAG CTG GAA ATC AAA
 Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
 100 105

(2) INFORMATION FOR SEQ ID NO: 40:

10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:399 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear

15 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse

20 (ix) FEATURE:
 (A) NAME/KEY:Clone 3GB1
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:40:

25 CTG TCG GTA ACT TCA GGG GTC TAC TCA GAG GTT CAG CTC GAG CAG TCT 48
 Leu Ser Val Thr Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser
 -5 1 5

30 GGG ACT GTG CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG TCC TGC AAG 96
 Gly Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys
 10 15 20

35 GCT TCG GGC TAC ACC TTT AAC AGC TAC TGG ATG CAC TGG GTA AAA CAG 144
 Ala Ser Gly Tyr Thr Phe Asn Ser Tyr Trp Met His Trp Val Lys Gln
 25 30 35

40 AGG CCT GGA CAG GGT CTG GAA TGG ATT GGC GCG ATT TAT CCT GGA AAT 192
 Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
 40 45 50 55

45 AGT GAT ATT AGC TAC AGC CAG AAC TTT AAG GAC AGG GCC AAA CTG ACT 240
 Ser Asp Ile Ser Tyr Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu Thr
 60 65 70

50 GCC GTC ACA TCC ACC AGC ACT GCC TAC ATG GAA CTC AGA AGC CTG ACA 288
 Ala Val Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr
 75 80 85

55 AAT GAG GAC TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA TAT GAT TAC 336
 Asn Glu Asp Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu Tyr Asp Tyr
 90 95 100

60 GAC ACC CTG GAC TAC TGG GGT CAA GGA ACC TCA GTC ACC GTC TCC TCA 384
 Asp Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
 105 110 115

65 GCC AAA ACG ACA CCC 399
 Ala Lys Thr Thr Pro
 120

(2) INFORMATION FOR SEQ ID NO: 41:

5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:402 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear

10 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse

15 (ix) FEATURE:
 (A) NAME/KEY:Clone 17GB7
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 41:

ATT	GTG	TCG	GTA	ACT	TCA	GGG	GTC	TAC	TCA	GAG	GTT	CAG	CTC	GAG	CAG	48	
Ile	Leu	Ser	Val	Thr	Ser	Gly	Val	Tyr	Ser	Glu	Val	Gln	Leu	Gln	Gln		
-10							-5					1			5		
20	TCT	GGG	ACT	GTG	CTG	GCA	AGG	CCT	GGG	GCT	TCA	GTG	AAG	ATG	TCC	TGC	96
Ser	Gly	Thr	Val	Leu	Ala	Arg	Pro	Gly	Ala	Ser	Val	Lys	Met	Ser	Cys		
	10							15					20				
25	AAG	GCT	TCG	GGC	TAC	ACC	TTT	AAC	AGC	TAC	TGG	ATG	CAC	TGG	GTA	AAA	144
Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Asn	Ser	Tyr	Trp	Met	His	Trp	Val	Lys		
	25						30					35					
30	CAG	AGG	CCT	GGG	CAG	GGT	CTG	GAA	TGG	ATT	GGC	GCG	ATT	TAT	CCT	GGA	192
Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	Gly	Ala	Ile	Tyr	Pro	Gly		
	40					45					50						
35	AAT	AGT	GAT	ATT	AGC	TAC	AGC	CAG	AAC	TTT	AAG	GAC	AGG	GCC	AAA	CTG	240
Asn	Ser	Asp	Ile	Ser	Tyr	Ser	Gln	Asn	Phe	Lys	Asp	Arg	Ala	Lys	Leu		
	55				60			65			70						
40	ACT	GCC	GTC	ACA	TCC	ACC	AGC	ACT	GCC	TAC	ATG	GAA	CTC	AGA	AGC	CTG	288
Thr	Ala	Val	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	Met	Glu	Leu	Arg	Ser	Leu		
							75		80			85					
45	ACA	AAT	GAG	GAC	TCT	GCG	GTC	TAT	TTC	TGT	ACA	AAA	GAG	GAA	TAT	GAT	336
Thr	Asn	Glu	Asp	Ser	Ala	Val	Tyr	Phe	Cys	Thr	Lys	Glu	Glu	Tyr	Asp		
					90			95			100						
50	TAC	GAC	ACC	CTG	GAC	TAC	TGG	GGT	CAA	GGA	ACC	TCA	GTC	ACC	GTC	TCC	384
Tyr	Asp	Thr	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser		
						105		110			115						
55	TCA	GCC	AAA	ACG	ACA	CCC										402	
Ser	Ala	Lys	Thr	Thr	Pro												
			120														

(2) INFORMATION FOR SEQ ID NO: 42:

50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:438 base pairs
 (B) TYPE:nucleic acid

		(C) STRANDEDNESS:double		
		(D) TOPOLOGY:linear		
5	(ii)	MOLECULE TYPE:mRNA		
	(iii)	HYPOTHETICAL:no		
	(iv)	ANTISENSE:no		
	(vi)	ORIGINAL SOURCE:		
		(A) ORGANISM:mouse		
10	(ix)	FEATURE:		
		(A) NAME/KEY:Clone 20GA2		
	(xi)	SEQUENCE DESCRIPTION:SEQ ID NO:42:		
	ATG GAG TTC GGG CTA AAC TGG GTT TTC CTT GTA ACA CTT TTA AAT GGT			
	Met Glu Phe Gly Leu Asn Trp Val Phe Leu Val Thr Leu Leu Asn Gly			
	15	-15	-10	-5
15	ATC CAG TGT GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC TTG GTA CAG			
	Ile Gln Cys Glu Val Lys Leu Val Glu Ser Gly Gly Leu Val Gln			
	1	5	10	15
20	CCT GGG GGT TCT CTC AGA CTC TCC TGT GCA ACT TCT GGG TTA ACC TTC			
	Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr Phe			
	15	20	25	30
25	ACT GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT CCA GGA AAG GAA CTT			
	Thr Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Lys Glu Leu			
	30	35	40	45
30	GAA TGG TTG GGT TTT ATT AGA AAC AAA GCT AAT CTT TAC ACA ACA GAC			
	Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr Asp			
	50	55	60	65
35	TAC AGT GCA TCT GTG AAG GGT CGG TTC ACC ATC TCC AGA CAT AAT CCC			
	Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro			
	65	70	75	80
40	CAA AGC ATC CTC TAT CTT CAA ATG AAC ACC CTG ACA ACT GAG GAC AGT			
	Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Thr Glu Asp Ser			
	80	85	90	95
45	GCC ACT TAT TAC TGT GCA AGA GAT AGG GGG GGG AGG GAC TGG TAC TTC			
	Ala Thr Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Arg Asp Trp Tyr Phe			
	95	100	105	110
50	GAT GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC TCC TCA GCC AAA ACG			
	Asp Val Trp Gly Ala Gly Thr Thr Val Val Ser Ser Ala Lys Thr			
	110	115	120	125
55	ACA CCC			
	Thr Pro			
			438	

(2) INFORMATION FOR SEQ ID NO: 43:

50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:411 base pairs
(B) TYPE:nucleic acid
(C) STRANDEDNESS:double
(D) TOPOLOGY:linear

5 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse
 (ix) FEATURE:
 (A) NAME/KEY:Clone 27GA5
 10 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 43:

10 CTT GTA ACA CGT TTA AAT GGT ATC CAG TGT GAG GTG AAG CTG GTG GAG 48
 Leu Val Thr Arg Leu Asn Gly Ile Gln Cys Glu Val Lys Leu Val Glu
 -10 -5 1 5

15 TCT GGA GGA GGC TTG GTA CAG CCT GGG GGT TCT CTG AGA CTC TCC TGT 96
 Ser Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
 10 15 20

20 GCA ACT TCT GGG TTC ACC TTC ACT GAT TAC TAC ATG AAC TGG GTC CGC 144
 Ala Thr Ser Gly Phe Thr Phe Thr Asp Tyr Tyr Met Asn Trp Val Arg
 25 30 35

CAG CCT CCA GGA AAG GCA CTT GAG TGG TTG GGT TTT ATT AGA AAC AAA 192
 Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys
 40 45 50

25 GCT AAT TAT TAC ACA ACA GAG TAC AGT GCA TCT GTG AAG GGT CGG TTC 240
 Ala Asn Tyr Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe
 55 60 65 70

30 ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC CTC TAT CTT CAA ATG AAC 288
 Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile Leu Gln Met Asn Thr Leu
 75 80 85

35 ACC CTG AGA GCT GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA GAT GGG 336
 Thr Leu Arg Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Asp Gly
 90 95 100

40 ACC GTC TCC TCA GCC AAA ACG ACA CCC 411
 Thr Val Ser Ser Ala Lys Thr Thr Pro
 120 125

(2) INFORMATION FOR SEQ ID NO: 44:

45 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH:354 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear
 50 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse

(ix) FEATURE:

(A) NAME/KEY:Clone 3KB11

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:44:

GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CCT CTG 48
 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Leu
 5 10 15

GGG CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC AAA AGT GTG CAG TTA 96
 Gly Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Gln Leu
 20 25 30

CAT CTG GCT ATA GTT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG 144
 His Leu Ala Ile Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln
 35 40 45

CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC 192
 Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val
 50 55 60

CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC 240
 Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn
 65 70 75 80

ATC CAT CCT GTG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC 288
 Ile His Pro Val Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His
 85 90 95

ATT AGG GTA GCT TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 336
 Ile Arg Val Ala Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

CGG GCT GAT GCT GCA CCA
 Arg Ala Asp Ala Ala Pro 354
 115

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH:438 base pairs
- (B) TYPE:nucleic acid
- (C) STANDEDNESS:double
- (D) TOPOLOGY:linear

(ii) MOLECULE TYPE:mRNA

(iii) HYPOTHETICAL:no

(iv) ANTISENSE:no

(vi) ORIGINAL SOURCE:

- (A) ORGANISM:mouse

(ix) FEATURE:

- (A) NAME/KEY:Clone 17KB1

(xi) SEQUENCE DESCRIPTION:SEQ ID NO: 45:

CTA TGG GTA CTG CTG CTC TGG GTT CCA GGT TCC ACT GGT GAC ATT GTG 48
 Leu Trp Val Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Val
 -10 -5 1

CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG CAG AGG GCC 96
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 5 10 15

TCC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT GGC TAT AGT 144
 Ser Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser
 20 25 30 35

10 TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC AGA CTC CTC 192
 Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu
 40 45 50

ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC CCT GCC AGG TTC AGT 240
 Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser
 15 55 60 65

GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT CCT GTG GAG 288
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu
 70 75 80

20 GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT AGG GGA GCT TAC 336
 Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg Gly Ala Tyr
 85 90 95

ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA CGG GCT GAT GCT GCA 384
 Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
 25 100 105 110 115

CCA ACT GTA TCC ATC TTC CCA CCA TCC AGT AAG CTT GGG AAA CGG TTC 432
 Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Lys Leu Gly Lys Arg Phe
 30 120 125 130

GCA CCG 438
 Ala Pro

35 (2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 417 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:double
 (D) TOPOLOGY:linear

40 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse

45 (ix) FEATURE:
 (A) NAME/KEY:Clone 20KB1
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:46:

50 GGCCGCG GTGAGAACCG TTGGGAATTC ATG GAG ACA GAC ACA CTC CTG 48
 Met Glu Thr Asp Thr Leu Leu
 -20 -15

5 CTA TGG GTA CTG CTG CTC TGG GTT CCA GGT TCC ACT GGT GAC ATT GTG 96
 Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Val
 -10 -5 1
 10 CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG CAG AGG GCC 144
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 5 10 15
 15 ACC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT GCC TAT AGT 192
 Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser
 20 25 30
 20 TAT ATG CAC TGG AAC CAA CAG AGA CCA GGA CAG CCA CCC AGA CTC CTC 240
 Tyr Met His Trp Asn Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu
 35 40 45
 25 ATC TAT CTT GTA TCC AAC CTA GAC TCT GGG GTC CCT GCC AGG TTC AGT 288
 Ile Tyr Leu Val Ser Asn Leu Asp Ser Gly Val Pro Ala Arg Phe Ser
 50 55 60 65
 30 GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT CCT GTG GAG 336
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu
 70 75 80
 35 GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT GAG GGA GCT TAC 384
 Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Glu Gly Ala Tyr
 85 90 95
 40 ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA 417
 Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
 100 105
 45 (2) INFORMATION FOR SEQ ID NO: 47:
 (i) SEQUENCE CHARACTERISTICS:
 35 (A) LENGTH: 420 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear
 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 40 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse
 (ix) FEATURE:
 (A) NAME/KEY:Clone 27KA2
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO: 47:
 45 GCGGCCGCGG TGAGAACCGT TTGGGAATTC ATC GAG ACA CAG TCC CAG 48
 Met Glu Thr Gln Ser Gln
 -20 -15
 50 GTC TTT GTA TTC GTG TTT CTC TGG TTG TCT GGT GTT GAC GGA GAC ATT 96
 Val Phe Val Phe Val Phe Leu Trp Leu Ser Gly Val Asp Gly Asp Ile
 -10 -5 1

5 GTG ATG ACC CAG TCT CAC AAA TTC ATG TCC ACA TCA GTA GGA GAC AGG 144
 Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly Asp Arg
 5 10 15

10 GTC AGT ATC ACC TGC AAG GCC AGT CAG GAT GTG AAT ACT GCT GTA GCC 192
 Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala
 20 25 30

15 TGG TAT CAA CAG AAA CCA GGA CAA TCT CCT AAA CTA CTG CTT TAC TCG 240
 Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Leu Tyr Ser
 35 40 45

20 GCA TCC TAC CGG TAC ACT GGA GTC CCT GAT CAC TTC ACT GGC AGT GGA 288
 Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp His Phe Thr Gly Ser Gly
 55 60 65

25 TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC GGT GTG CAG GCT GAA GAC 336
 Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Val Gln Ala Glu Asp
 70 75 80

30 CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT AGT CCT CCT CTC ACG TTC 384
 Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Leu Thr Phe
 85 90 95

35 GGT GCT GGG ACC AAG CTG GAA CTG AAA CGG GCT GAT 420
 Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
 100 105 110

(2) INFORMATION FOR SEQ ID NO: 48:

30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 360 base pairs
 (B) TYPE:nucleic acid
 (C) STRANDEDNESS:single
 (D) TOPOLOGY:linear

35 (ii) MOLECULE TYPE:mRNA
 (iii) HYPOTHETICAL:no
 (iv) ANTISENSE:no
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM:mouse

40 (ix) FEATURE:
 (A) NAME/KEY:Clone 23KA26
 (xi) SEQUENCE DESCRIPTION:SEQ ID NO:48

45 GGT GTT GAC GGA GAC ATT GTG ATG ACA CAG TCT CAC AAA TTC ATG TCC 48
 Gly Val Asp Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser
 1 5 10

50 ACA TCA GTT GGA GAC AGG GTC ACC ATC ACC TGC AAG GCC AGT CAG GAT 96
 Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
 15 20 25

55 GTG ACT ACT GAT GTA GCC TGG TAT CAA CAG AAA CCA CGA CAA TCT CCT 144
 Val Thr Thr Asp Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro
 30 35 40

	AAA CTA CTG ATT TAC TCG GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT	192
5	Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp	
	45 50 55	
	CGC TTC ACT GGC AGT GGA TCT GGG ACG GAT TTC ACT TTC ACC ATC AGC	240
	Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser	
	60 65 70 75	
10	AGT GTG CAG GCT GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA CAT TAT	288
	Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr	
	80 85 90	
	AGT ACT GCG TGG ACG TTC GGT GGT GGC ACC AAG CTG GAA ATC AAA CCG	336
15	Ser Thr Ala Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg	
	95 100 105	
	GCT GAT GCT GCA CCA ACT GTA TCC	360
	Ala Asp Ala Ala Pro Thr Val Ser	
	110 115	

25 **Claims**

1. An immunoglobulin H chain variable region fragment which contains a hypervariable region CDR1 having an amino acid sequence selected from

(1) Ser Tyr Trp Met His;
Asp Tyr Tyr Met Asn; and
Asn Tyr Trp Met Gln.

a hypervariable region CDR2 having an amino acid sequence selected from

(2) Ala Ile Tyr Pro Gly Asn Ser
Asp Ile Ser Tyr Ser Gln Asn
Phe Lys Asp;
Phe Ile Arg Asn Lys Ala
Asn Leu Tyr Thr Thr Asp
Tyr Ser Ala Ser Val Lys
Gly;
Phe Ile Arg Asn Lys Ala
Asn Tyr Tyr Thr Thr Glu
Tyr Ser Ala Ser Val Lys
Gly; and
Ala Ile Tyr Pro Gly Asp
Gly Asp Thr Arg Tyr Thr
Gln Lys Phe Lys Gly.

and a hypervariable region CDR3 having an amino acid sequence selected from

5 (3) Glu Glu Tyr Asp Tyr Asp
Thr Leu Asp Tyr;
Asp Arg Gly Gly Arg Asp
Trp Tyr Phe Asp Val;
Asp Gly Phe Leu Arg Asp
10 Trp Tyr Phe Asp Val; and
Ser Gly Tyr Tyr Gly Ser
Phe Val Gly Phe Ala Tyr .

15

2. An immunoglobulin H chain variable region fragment having the following amino acid sequence

20 Glu Val Gln Leu Gln Gln Ser Gly Thr Val
Leu Ala Arg Pro Gly Ala Ser Val Lys Met
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn
Ser Tyr Trp Met His Trp Val Lys Gln Arg
25 Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala
Ile Tyr Pro Gly Asn Ser Asp Ile Ser Tyr
Ser Gln Asn Phe Lys Asp Arg Ala Lys Leu
30 Thr Ala Val Thr Ser Thr Ser Thr Ala Tyr
Met Glu Leu Arg Ser Leu Thr Asn Glu Asp
Ser Ala Val Tyr Phe Cys Thr Lys Glu Glu
35 Tyr Asp Tyr Asp Thr Leu Asp Tyr Trp Gly
Gln Gly Thr Ser Val Thr Val Ser Ser .

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3. An immunoglobulin H chain variable region fragment having the following amino acid sequence

5 Glu Val Lys Leu Val Glu Ser Gly Gly Gly
Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr
Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro
Pro Gly Lys Ala Leu Glu Trp Leu Gly Phe
Ile Arg Asn Lys Ala Asn Tyr Tyr Thr Thr
Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe
Thr Ile Ser Arg Asp Asn Ser Gln Ser Ile
15 Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala
Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg
Asp Gly Phe Leu Arg Asp Trp Tyr Phe Asp
Val Trp Gly Ala Gly Thr Thr Val Thr Val
20 Ser Ser.

25 4. An immunoglobulin H chain variable region fragment having the following amino acid sequence

30 Glu Val Lys Leu Val Glu Ser Gly Gly Gly
Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
Ser Cys Ala Thr Ser Gly Leu Thr Phe Thr
Asp Tyr Tyr Met Asn Trp Val Arg Gln Pro
Pro Gly Lys Glu Leu Glu Trp Leu Gly Phe
Ile Arg Asn Lys Ala Asn Leu Tyr Thr Thr
Asp Tyr Ser Ala Ser Val Lys Gly Arg Phe
Thr Ile Ser Arg Asp Asn Pro Gln Ser Ile
40 Leu Tyr Leu Gln Met Asn Thr Leu Thr Thr
Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg
Asp Arg Gly Gly Arg Asp Trp Tyr Phe Asp
Val Trp Gly Ala Gly Thr Thr Val Thr Val
45 Ser Ser.

50

55

5. An immunoglobulin H chain variable region fragment having the following amino acid sequence

5 Glu Val Gln Leu Gln Gln Ser Gly Ala Glu
 Leu Ala Arg Pro Gly Ala Ser Val Asn Leu
 Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
 Asn Tyr Trp Met Gln Trp Val Lys Gln Arg
 10 Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala
 Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr
 Thr Gln Lys Phe Lys Gly Lys Ala Thr Leu
 Thr Ala Ala Lys Ser Ser Ser Thr Ala Tyr
 15 Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
 Ser Ala Val Tyr Tyr Cys Ala Arg Ser Gly
 Tyr Tyr Gly Ser Phe Val Gly Phe Ala Tyr
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 20 Ala .

25 6. DNA and RNA fragments each encoding an immunoglobulin H chain variable region fragment which contains a base sequence encoding a hypervariable region CDR1 having an amino acid sequence selected from

30 (1) Ser Tyr Trp Met His;
 Asp Tyr Tyr Met Asn; and
 Asn Tyr Trp Met Gln ,

35 a base sequence encoding a hypervariable region CDR2 having an amino acid sequence selected from

40 (2) Ala Ile Tyr Pro Gly Asn Ser
 Asp Ile Ser Tyr Ser Gln Asn
 Phe Lys Asp;
 Phe Ile Arg Asn Lys Ala
 Asn Leu Tyr Thr Thr Asp
 Tyr Ser Ala Ser Val Lys
 45 Gly;
 Phe Ile Arg Asn Lys Ala
 Asn Tyr Tyr Thr Thr Glu
 Tyr Ser Ala Ser Val Lys
 Gly; and
 Ala Ile Tyr Pro Gly Asp
 Gly Asp Thr Arg Tyr Thr
 50 Glu Lys Phe Lys Gly .

a base sequence encoding a hypervariable region CDR3 having an amino acid sequence selected from

(3) Glu Glu Tyr Asp Tyr Asp
5 Thr Leu Asp Tyr;
Asp Arg Gly Gly Arg Asp
Trp Tyr Phe Asp Val;
Asp Gly Phe Leu Arg Asp
10 Trp Tyr Phe Asp Val; and
Ser Gly Tyr Tyr Gly Ser
Phe Val Gly Phe Ala Tyr .

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7. An immunoglobulin H chain variable region fragment having following base sequence

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GAG GTT CAG CTC CAG CAG TCT GGG ACT GTG
CTG GCA AGG CCT GGG GCT TCA GTG AAG ATG
TCC TGC AAG GCT TCG GGC TAC ACC TTT AAC
AGC TAC TGG ATG CAC TGG GTA AAA CAG AGG
CCT GGA CAG GGT CTG GAA TGG ATT GGC GCG
ATT TAT CCT GGA AAT AGT GAT ATT AGC TAC
AGC CAG AAC TTT AAG GAC AGG GCC AAA CTG
ACT GCC GTC ACA TCC ACC AGC ACT GCC TAC
ATG GAA CTC AGA AGC CTG ACA AAT GAG GAC
TCT GCG GTC TAT TTC TGT ACA AAA GAG GAA
TAT GAT TAC GAC ACC CTG GAC TAC TGG GGT
CAA GGA ACC TCA GTC ACC GTC TCC TCA.

8. An immunoglobulin H chain variable region fragment having the following base sequence

5 GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC
TTG GTA CAG CCT GGG GGT TCT CTC AGA CTC
TCC TGT GCA ACT TCT GGG TTA ACC TTC ACT
GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT
CCA GGA AAG GAA CTT GAA TGG TTG GGT TTT
10 ATT AGA AAC AAA GCT AAT CTT TAC ACA ACA
GAC TAC AGT GCA TCT GTG AAG GGT CGG TTC
ACC ATC TCC AGA GAT AAT CCC CAA AGC ATC
CTC TAT CTT CAA ATG AAC ACC CTG ACA ACT
GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA
GAT AGG GGG GGG AGG GAC TGG TAC TTC GAT
GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC
15 TCC TCA .
20

25 9. An immunoglobulin H chain variable region fragment having the following base sequence

30 GAG GTG AAG CTG GTG GAG TCT GGA GGA GGC
TTG GTA CAG CCT GGG GGT TCT CTG AGA CTC
TCC TGT GCA ACT TCT GGG TTC ACC TTC ACT
GAT TAC TAC ATG AAC TGG GTC CGC CAG CCT
CCA GGA AAG GCA CTT GAG TGG TTG GGT TTT
35 ATT AGA AAC AAA GCT AAT TAT TAC ACA ACA
GAG TAC AGT GCA TCT GTG AAG GGT CGG TTC
ACC ATC TCC AGA GAT AAT TCC CAA AGC ATC
CTC TAT CTT CAA ATG AAC ACC CTG AGA GCT
GAG GAC AGT GCC ACT TAT TAC TGT GCA AGA
40 GAT GGG TTC CTA CGG GAC TGG TAC TTC GAT
GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC
45 TCC TCA .

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10. An immunoglobulin H chain variable region fragment having the following base sequence

5 GAG GTT CAG CTC CAG CAG TCT GGG GCT GAA
 CTG GCA AGA CCT GGG GCT TCA GTG AAC TTG
 TCC TGC AAG GCT TCT GGC TAC ACC TTT ACT
 AAC TAC TGG ATG CAG TGG GTA AAA CAG AGG
 10 CCT GGA CAG GGT CTG GAA TGG ATT GGG GCT
 ATT TAT CCT GGA GAT GGT GAT ACT AGG TAC
 ACT CAG AAG TTC AAG GGC AAG GCC ACA TTG
 ACT GCA GCT AAA TCC TCC AGC ACA GCC TAC
 15 ATG CAA CTC AGC AGC TTG GCA TCT GAG GAC
 TCT GCG GTC TAT TAC TGT GCA AGA TCG GGC
 TAC TAT GGT AGC TTC GTT GGG TTT GCT TAC
 TGG GGC CAA GGG ACT CTG GTC ACT GTC TCT
 20 GCA .

25 11. An immunoglobulin L chain variable region fragment which contains a hypervariable region CDR1 having an amino acid sequence selected from

30 (1) Tyr Arg Ala Ser Lys Ser Val
 Gln Leu His Leu Ala Ile Val
 Tyr Met His;
 Tyr Arg Ala Ser Lys Ser Val
 Ser Thr Ser Gly Tyr Ser Tyr
 35 Met His;
 Lys Ala Ser Gln Asp Val Asn
 Thr Ala Val Ala; and
 40 Lys Ala Ser Gln Asp Val Thr
 Thr Asp Val Ala .

a hypervariable region CDR2 having an amino acid sequence selected from

45 (2) Leu Val Ser Asn Leu Glu Ser;
 Leu Val Ser Asn Leu Asp Ser; and
 Ser Ala Ser Tyr Arg Tyr Thr,
 50

and a hypervariable region CDR3 having an amino acid sequence selected from

(3) Gln His Ile Arg Val Ala Tyr
5 Thr;
Gln His Ile Arg Gly Ala Tyr
10 Thr;
Gln His Ile Glu Gly Ala Tyr
15 Thr;
Gln Gln His Tyr Ser Pro Pro
Leu Thr; and
Gln Gln His Tyr Ser Thr Ala
Trp Thr .

20 12. An immunoglobulin L chain variable region fragment having the following amino acid sequence

25 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
Leu Ala Val Ser Pro Leu Gly Gln Arg Ala
Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val
Gln Leu His Leu Ala Ile Val Tyr Met His
Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro
30 Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu
Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn
Ile His Pro Val Glu Glu Asp Ala Ala
35 Thr Tyr Tyr Cys Gln His Ile Arg Val Ala
Tyr Thr Phe Gly Gly Thr Lys Leu Glu
Ile Lys .

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13. An immunoglobulin L chain variable region fragment having the following amino acid sequence

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
5 Leu Ala Val Ser Leu Gly Gln Arg Ala Ser
Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser
10 Thr Ser Gly Tyr Ser Tyr Met His Trp Asn
Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu
Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
Ser Gly Thr Asp Phe Thr Leu Asn Ile His
15 Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr
Tyr Cys Gln His Ile Arg Gly Ala Tyr Thr
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys.

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14. An immunoglobulin L chain variable region fragment having the following amino acid sequence

25 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr
Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser
30 Thr Ser Gly Tyr Ser Tyr Met His Trp Asn
Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu
Leu Ile Tyr Leu Val Ser Asn Leu Asp Ser
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
Ser Gly Thr Asp Phe Thr Leu Asn Ile His
35 Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr
Tyr Cys Gln His Ile Glu Gly Ala Tyr Thr
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys.

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15. An immunoglobulin L chain variable region fragment having the following amino acid sequence

Asp Ile Val Met Thr Gln Ser His Lys Phe
5 Met Ser Thr Ser Val Gly Asp Arg Val Ser
Ile Thr Cys Lys Ala Ser Gln Asp Val Asn
Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro
10 Gly Gln Ser Pro Lys Leu Leu Leu Tyr Ser
Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp
His Phe Thr Gly Ser Gly Ser Gly Thr Asp
Phe Thr Phe Thr Ile Ser Gly Val Gln Ala
15 Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
His Tyr Ser Pro Pro Leu Thr Phe Gly Ala
Gly Thr Lys Leu Glu Leu Lys .

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16. An immunoglobulin L chain variable region fragment having the following amino acid sequence

Asp Ile Val Met Thr Gln Ser His Lys Phe
25 Met Ser Thr Ser Val Gly Asp Arg Val Thr
Ile Thr Cys Lys Ala Ser Gln Asp Val Thr
Thr Asp Val Ala Trp Tyr Gln Gln Lys Pro
30 Arg Gln Ser Pro Lys Leu Leu Ile Tyr Ser
Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
35 Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
His Tyr Ser Thr Ala Trp Thr Phe Gly Gly
Gly Thr Lys Leu Glu Ile Lys .

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17. DNA and RNA fragments each encoding an immunoglobulin L chain variable region fragment which contains a base sequence encoding a hypervariable region CDR1 having an amino acid sequence selected from

5 (1) Tyr Arg Ala Ser Lys Ser Val
Gln Leu His Leu Ala Ile Val
Tyr Met His;
10 Tyr Arg Ala Ser Lys Ser Val
Ser Thr Ser Gly Tyr Ser Tyr
Met His;
15 Lys Ala Ser Gln Asp Val Asn
Thr Ala Val Ala; and
Lys Ala Ser Gln Asp Val Thr
Thr Asp Val Ala ,

20 a base sequence encoding a hypervariable region CDR2 having an amino acid sequence selected from

25 (2) Leu Val Ser Asn Leu Glu Ser;
Leu Val Ser Asn Leu Asp Ser; and
Ser Ala Ser Tyr Arg Tyr Thr ,

and a base sequence encoding a hypervariable region CDR3 having an amino acid sequence selected from

30 (3) Gln His Ile Arg Val Ala Tyr
Thr;
Gln His Ile Arg Gly Ala Tyr
35 Thr;
Gln His Ile Glu Gly Ala Tyr
Thr;
Gln Gln His Tyr Ser Pro Pro
40 Leu Thr; and
Gln Gln His Tyr Ser Thr Ala
Trp Thr .

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18. An immunoglobulin L chain variable region fragment having the following base sequence

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GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC
TTA GCT GTA TCT CCT CTG GGG CAG AGG GCC
ACC ATC TCA TAC AGG GCC AGC AAA AGT GTG
CAG TTA CAT CTG GCT ATA GTT TAT ATG CAC
TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC
AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA
GAA TCT GGG GTC CCT GCC AGG TTC AGT GGC
AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC
ATC CAT CCT GTG GAG GAG GAT GCT GCA
ACC TAT TAC TGT CAG CAC ATT AGG GTA GCT
TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA
ATA AAA .

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19. An immunoglobulin L chain variable region fragment having the following base sequence

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GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC
TTA GCT GTA TCT CTG GGG CAG AGG GCC TCC
ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT
ACA TCT GGC TAT AGT TAT ATG CAC TGG AAC
CAA CAG AAA CCA GGA CAG CCA CCC AGA CTC
CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT
GGG GTC CCT GCC AGG TTC AGT GGC AGT GGG
TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT
CCT GTG GAG GAG GAT GCT GCA ACC TAT
TAC TGT CAG CAC ATT AGG GGA GCT TAC ACG
TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA .

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20. An immunoglobulin L chain variable region fragment having the following base sequence

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GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC
 TTA GCT GTA TCT CTG GGG CAG AGG GCC ACC
 ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT
 ACA TCT GGC TAT AGT TAT ATG CAC TGG AAC
 CAA CAG AGA CCA GGA CAG CCA CCC AGA CTC
 CTC ATC TAT CTT GTA TCC AAC CTA GAC TCT
 GGG GTC CCT GCC AGG TTC AGT GGC AGT GGG
 TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT
 CCT GTG GAG GAG GAT GCT GCA ACC TAT
 TAC TGT CAG CAC ATT GAG GGA GCT TAC ACG
 TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA .

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21. An immunoglobulin L chain variable region fragment having the following base sequence

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GAC ATT GTG ATG ACC CAG TCT CAC AAA TTC
 ATG TCC ACA TCA GTA GGA GAC AGG GTC AGT
 ATC ACC TGC AAG GCC AGT CAG GAT GTG AAT
 ACT GCT GTA GCC TGG TAT CAA CAG AAA CCA
 GGA CAA TCT CCT AAA CTA CTG CTT TAC TCG
 GCA TCC TAC CGG TAC ACT GGA GTC CCT GAT
 CAC TTC ACT GGC AGT GGA TCT GGG ACG GAT
 TTC ACT TTC ACC ATC AGC GGT GTG CAG GCT
 GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA
 CAT TAT AGT CCT CCT CTC ACG TTC GGT GCT
 GGG ACC AAG CTG GAA CTG AAA .

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22. An immunoglobulin L chain variable region fragment having the following base sequence

5 GAC ATT GTG ATG ACA CAG TCT CAC AAA TTC
ATG TCC ACA TCA GTT GGA GAC AGG GTC ACC
ATC ACC TGC AAG GCC AGT CAG GAT GTG ACT
ACT GAT GTA GCC TGG TAT CAA CAG AAA CCA
10 CGA CAA TCT CCT AAA CTA CTG ATT TAC TCG
GCA TCC TAT CGG TAC ACT GGA GTC CCT GAT
CGC TTC ACT GGC AGT GGA TCT GGG ACG GAT
TTC ACT TTC ACC ATC AGC AGT GTG CAG GCT
15 GAA GAC CTG GCA GTT TAT TAC TGT CAG CAA
CAT TAT AGT ACT GCG TGG ACG TTC GGT GGT
GGC ACC AAG CTG GAA ATC AAA .

20

23. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 2 and the immunoglobulin L chain variable region fragment according to claim 12.

25 24. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 2 and the immunoglobulin L chain variable region fragment according to claim 13.

30 25. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 3 and the immunoglobulin L chain variable region fragment according to claim 14.

35 26. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 4 and the immunoglobulin L chain variable region fragment according to claim 15.

40 27. An Fv region fragment comprising the immunoglobulin H chain variable region fragment according to claim 5 and the immunoglobulin L chain variable region fragment according to claim 16.

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FIG. I

Idio 3**Idio 17****Idio 20****Idio 27****Idio 33**

+	λ	K	G3	G2b	G2a	G1	M	A
+	λ	K	G3	G2b	G2a	G1	M	A
+	λ	K	G3	G2b	G2a	G1	M	A
+	λ	K	G3	G2b	G2a	G1	M	A
+	λ	K	G3	G2b	G2a	G1	M	A

FIG. 2

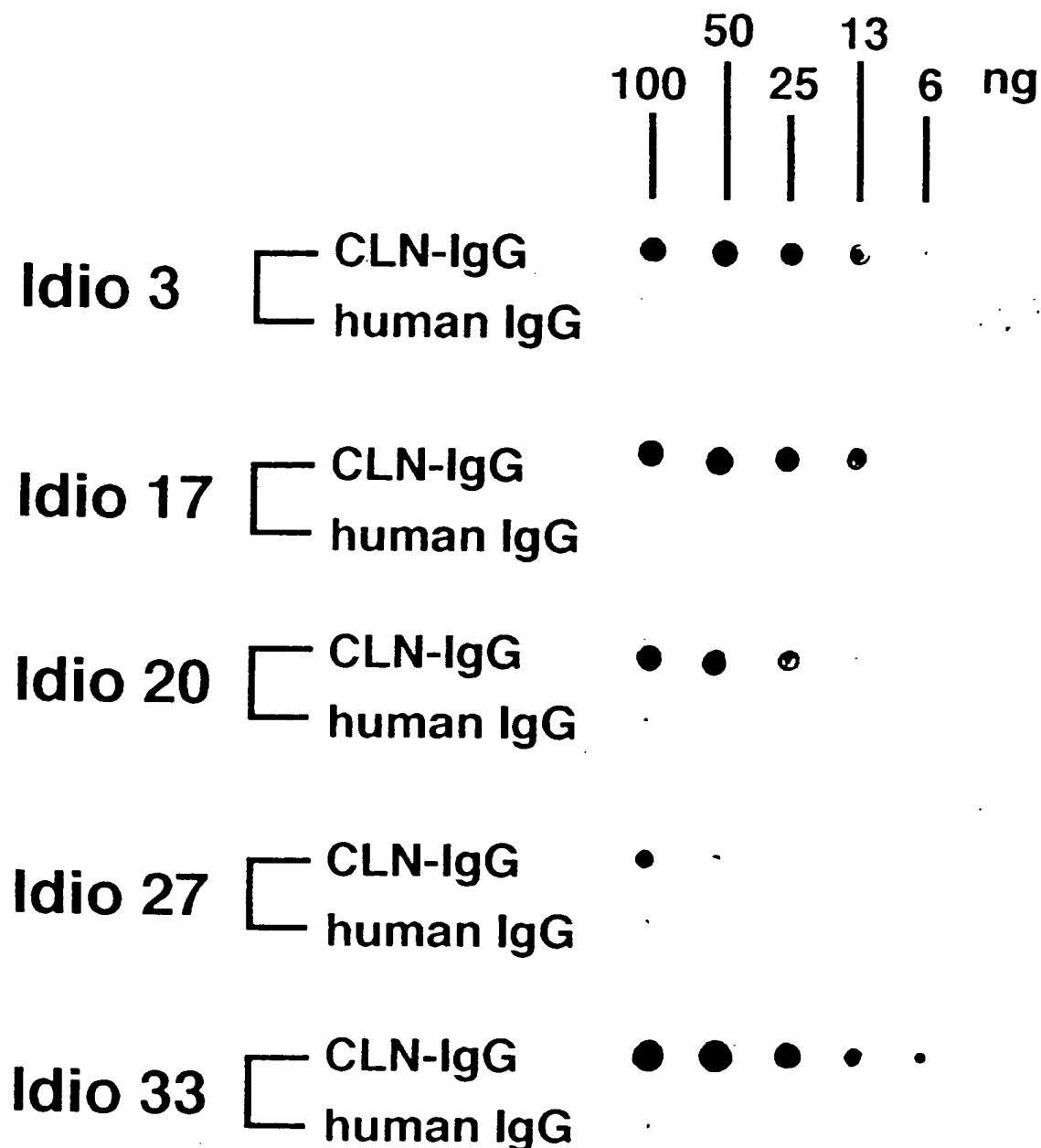


FIG. 3

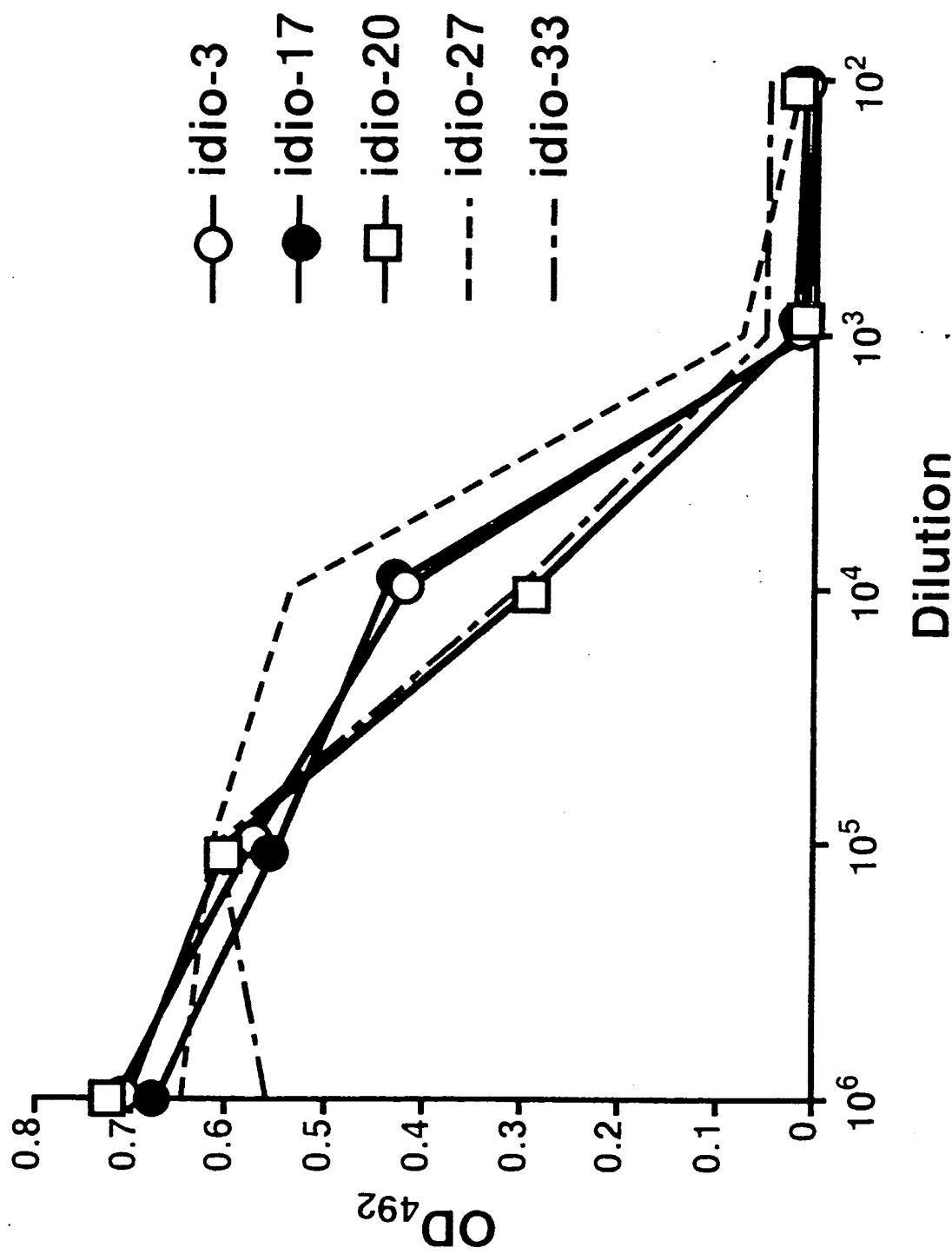


FIG. 4

3 17 20 27 33

F R 1	1	Glu	Glu	Glu	Glu	Glu	68	Lys	Lys	Thr	Thr	Thr
	2	Val	Val	Val	Val	Val	69	Leu	Leu	Ile	Ile	Leu
	3	Gln	Gln	Lys	Lys	Gln	70	Thr	Thr	Ser	Ser	Thr
	4	Leu	Leu	Leu	Leu	Leu	71	Ala	Ala	Arg	Arg	Ala
	5	Gln	Gln	Val	Val	Gln	72	Val	Val	Asp	Asp	Ala
	6	Gln	Gln	Glu	Glu	Gln	73	Thr	Thr	Asn	Asn	Lys
	7	Ser	Ser	Ser	Ser	Ser	74	Ser	Ser	Pro	Ser	Ser
	8	Gly	Gly	Gly	Gly	Gly	75	Thr	Thr	Gln	Gln	Ser
	9	Thr	Thr	Gly	Gly	Ala	76	Ser	Ser	Ser	Ser	Ser
	10	Val	Val	Gly	Gly	Glu	77	Thr	Thr	Ile	Ile	Thr
	11	Leu	Leu	Leu	Leu	Leu	78	Ala	Ala	Leu	Leu	Ala
	12	Ala	Ala	Val	Val	Ala	79	Tyr	Tyr	Tyr	Tyr	Tyr
	13	Arg	Arg	Gln	Gln	Arg	80	Met	Met	Leu	Leu	Met
	14	Pro	Pro	Pro	Pro	Pro	81	Glu	Glu	Gln	Gln	Gln
	15	Gly	Gly	Gly	Gly	Gly	82	Leu	Leu	Met	Met	Leu
	16	Ala	Ala	Gly	Gly	Ala	82A	Arg	Arg	Asn	Asn	Ser
	17	Ser	Ser	Ser	Ser	Ser	82B	Ser	Ser	Thr	Thr	Ser
	18	Val	Val	Leu	Leu	Val	82C	Leu	Leu	Leu	Leu	Leu
	19	Lys	Lys	Arg	Arg	Asn	83	Thr	Thr	Thr	Arg	Ala
	20	Met	Met	Leu	Leu	Leu	84	Asn	Asn	Thr	Ala	Ser
	21	Ser	Ser	Ser	Ser	Ser	85	Glu	Glu	Glu	Glu	Glu
	22	Cys	Cys	Cys	Cys	Cys	86	Asp	Asp	Asp	Asp	Asp
	23	Lys	Lys	Ala	Ala	Lys	87	Ser	Ser	Ser	Ser	Ser
	24	Ala	Ala	Thr	Thr	Ala	88	Ala	Ala	Ala	Ala	Ala
	25	Ser	Ser	Ser	Ser	Ser	89	Val	Val	Thr	Thr	Val
	26	Gly	Gly	Gly	Gly	Gly	90	Tyr	Tyr	Tyr	Tyr	Tyr
	27	Tyr	Tyr	Leu	Phe	Tyr	91	Phe	Phe	Tyr	Tyr	Tyr
	28	Thr	Thr	Thr	Thr	Thr	92	Cys	Cys	Cys	Cys	Cys
	29	Phe	Phe	Phe	Phe	Phe	93	Thr	Thr	Ala	Ala	Ala
	30	Asn	Asn	Thr	Thr	Thr	94	Lys	Lys	Arg	Arg	Arg
C D R 1	31	Ser	Ser	Asp	Asp	Asn	95	Glu	Glu	Asp	Asp	Ser
	32	Tyr	Tyr	Tyr	Tyr	Tyr	96	Glu	Glu	Arg	Gly	Gly
	33	Trp	Trp	Tyr	Tyr	Trp	97	Tyr	Tyr	Gly	Phe	Tyr
	34	Met	Met	Met	Met	Met	98	Asp	Asp	Gly	Leu	Tyr
F R 2	35	His	His	Asn	Asn	Gln	99	Tyr	Tyr	Arg	Arg	Gly
	36	Trp	Trp	Trp	Trp	Trp	100	Asp	Asp	Asp	Asp	Ser
	37	Val	Val	Val	Val	Val	100A	Thr	Thr	---	---	Phe
	38	Lys	Lys	Arg	Arg	Lys	100B	---	---	---	---	Val
	39	Gln	Gln	Gln	Gln	Gln	100C	---	---	---	---	Gly
	40	Arg	Arg	Pro	Pro	Arg	100D	---	---	---	---	---
	41	Pro	Pro	Pro	Pro	Pro	100E	---	---	---	---	---
	42	Gly	Gly	Gly	Gly	Gly	100F	---	---	---	---	---
	43	Gln	Gln	Lys	Lys	Gln	100G	---	---	---	---	---
	44	Gly	Gly	Glu	Ala	Gly	100H	---	---	---	---	---
	45	Leu	Leu	Leu	Leu	Leu	100I	---	---	Trp	Trp	---
	46	Glu	Glu	Glu	Glu	Glu	100J	---	---	Tyr	Tyr	---
	47	Trp	Trp	Trp	Trp	Trp	100K	Leu	Leu	Phe	Phe	Phe
	48	Ile	Ile	Leu	Leu	Ile	101	Asp	Asp	Asp	Asp	Ala
	49	Gly	Gly	Gly	Gly	Gly	102	Tyr	Tyr	Val	Val	Tyr
	50	Ala	Ala	Phe	Phe	Ala	103	Trp	Trp	Trp	Trp	Trp
	51	Ile	Ile	Ile	Ile	Ile	104	Gly	Gly	Gly	Gly	Gly
	52	Tyr	Tyr	Arg	Arg	Tyr	105	Gln	Gln	Ala	Ala	Gln
	52A	Pro	Pro	Asn	Asn	Pro	106	Gly	Gly	Gly	Gly	Gly
	52B	---	---	Lys	Lys	---	107	Thr	Thr	Thr	Thr	Thr
	52C	---	---	Ala	Ala	---	108	Ser	Ser	Thr	Thr	Leu
	53	Gly	Gly	Asn	Asn	Gly	109	Val	Val	Val	Val	Val
	54	Asn	Asn	Leu	Tyr	Asp	110	Thr	Thr	Thr	Thr	Thr
	55	Ser	Ser	Tyr	Tyr	Gly	111	Val	Val	Val	Val	Val
	56	Asp	Asp	Thr	Thr	Asp	112	Ser	Ser	Ser	Ser	Ser
	57	Ile	Ile	Thr	Thr	Thr	113	Ser	Ser	Ser	Ser	Ala
	58	Ser	Ser	Asp	Glu	Arg						
	59	Tyr	Tyr	Tyr	Tyr	Tyr						
	60	Ser	Ser	Ser	Ser	Thr						
	61	Gln	Gln	Ala	Ala	Gln						
	62	Asn	Asn	Ser	Ser	Lys						
	63	Phe	Phe	Val	Val	Phe						
	64	Lys	Lys	Lys	Lys	Lys						
	65	Asp	Asp	Gly	Gly	Gly						
	66	Arg	Arg	Arg	Arg	Lys						
	67	Ala	Ala	Phe	Phe	Ala						

FIG. 5

3 17 20 27 33

F R 1	1	Asp	Asp	Asp	Asp	Asp	65	Ser	Ser	Ser	Ser	Ser	Ser	
	2	Ile	Ile	Ile	Ile	Ile	66	Gly	Gly	Gly	Gly	Gly	Gly	
	3	Val	Val	Val	Val	Val	67	Gly	Ser	Ser	Ser	Ser	Ser	
	4	Leu	Leu	Leu	Met	Met	68	Gly	Gly	Gly	Gly	Gly	Gly	
	5	Thr	Thr	Thr	Thr	Thr	69	Thr	Thr	Thr	Thr	Thr	Thr	
	6	Gln	Gln	Gln	Gln	Gln	70	Asp	Asp	Asp	Asp	Asp	Asp	
	7	Ser	Ser	Ser	Ser	Ser	71	Phe	Phe	Phe	Phe	Phe	Phe	
	8	Pro	Pro	Pro	His	His	72	Thr	Thr	Thr	Thr	Thr	Thr	
	9	Ala	Ala	Ala	Lys	Lys	73	Leu	Leu	Leu	Phe	Phe	Phe	
	10	Ser	Ser	Ser	Phe	Phe	74	Asn	Asn	Asn	Thr	Thr	Thr	
	11	Leu	Leu	Leu	Met	Met	75	Ile	Ile	Ile	Ile	Ile	Ile	
	12	Ala	Ala	Ala	Ser	Ser	76	His	His	His	Ser	Ser	Ser	
	13	Val	Val	Val	Thr	Thr	77	Pro	Pro	Pro	Ser	Ser	Ser	
	14	Ser	Ser	Ser	Ser	Ser	78	Val	Val	Val	Val	Val	Val	
	15	Pro	Leu	Leu	Val	Val	79	Glu	Glu	Glu	Gln	Gln	Gln	
	16	Leu	Gly	Gly	Gly	Gly	80	Glu	Glu	Glu	Ala	Ala	Ala	
	17	Gly	Gln	Gln	Asp	Asp	81	Glu	Glu	Glu	Glu	Glu	Glu	
	18	Gln	Arg	Arg	Arg	Arg	82	Asp	Asp	Asp	Asp	Asp	Asp	
	19	Arg	Ala	Ala	Val	Val	83	Ala	Ala	Ala	Leu	Leu	Leu	
	20	Ala	Ser	Thr	Ser	Thr	84	Ala	Ala	Ala	Ala	Ala	Ala	
	21	Thr	Ile	Ile	Ile	Ile	85	Thr	Thr	Thr	Val	Val	Val	
	22	Ile	Ser	Ser	Thr	Thr	86	Tyr	Tyr	Tyr	Tyr	Tyr	Tyr	
	23	Ser	---	---	Cys	Cys	87	Tyr	Tyr	Tyr	Tyr	Tyr	Tyr	
C D R 1	24	Tyr	Tyr	Tyr	Lys	Lys	88	Cys	Cys	Cys	Cys	Cys	Cys	
	25	Arg	Arg	Arg	Ala	Ala	89	Gln	Gln	Gln	Gln	Gln	Gln	
	26	Ala	Ala	Ala	Ser	Ser	90	His	His	His	Gln	Gln	Gln	
	27	Ser	Ser	Ser	Gln	Gln	91	Ile	Ile	Ile	His	His	His	
	27A	Lys	Lys	Lys	---	---	92	Arg	Arg	Glu	Tyr	Tyr	Tyr	
	27B	Sér	Sér	Sér	---	---	93	Val	Gly	Gly	Ser	Ser	Ser	
	27C	Val	Val	Val	---	---	94	Ala	Ala	Ala	Pro	Thr	Thr	
	27D	Gln	Ser	Ser	---	---	95	---	---	---	Pro	Ala	Ala	
	27E	Leu	Thr	Thr	---	---	95A	---	---	---	---	---	---	
	27F	His	---	---	---	---	95B	---	---	---	---	---	---	
	1	28	Leu	Ser	Ser	Asp	Asp	95C	---	---	---	---	---	---
	29	Ala	Gly	Gly	Val	Val	95D	---	---	---	---	---	---	
	30	Ile	Tyr	Tyr	Asn	Thr	95E	---	---	---	---	---	---	
	31	Val	Ser	Ser	Thr	Thr	95F	---	---	---	---	---	---	
	32	Tyr	Tyr	Tyr	Ala	Asp	96	Tyr	Tyr	Tyr	Leu	Trp	Trp	
	33	Met	Met	Met	Val	Val	97	Thr	Thr	Thr	Thr	Thr	Thr	
	34	His	His	His	Ala	Ala	98	Phe	Phe	Phe	Phe	Phe	Phe	
F R 2	35	Trp	Trp	Trp	Trp	Trp	99	Gly	Gly	Gly	Gly	Gly	Gly	
	36	Asn	Asn	Asn	Tyr	Tyr	100	Gly	Gly	Gly	Ala	Gly	Gly	
	37	Gln	Gln	Gln	Gln	Gln	101	Gly	Gly	Gly	Gly	Gly	Gly	
	38	Gln	Gln	Gln	Gln	Gln	102	Thr	Thr	Thr	Thr	Thr	Thr	
	39	Lys	Lys	Arg	Lys	Lys	103	Lys	Lys	Lys	Lys	Lys	Lys	
	40	Pro	Pro	Pro	Pro	Pro	104	Leu	Leu	Leu	Leu	Leu	Leu	
	41	Gly	Gly	Gly	Gly	Arg	105	Glu	Glu	Glu	Glu	Glu	Glu	
	42	Gln	Gln	Gln	Gln	Gln	106	Ile	Ile	Ile	Ile	Ile	Ile	
	43	Pro	Pro	Pro	Ser	Ser	106A	---	---	---	---	---	---	
	44	Pro	Pro	Pro	Pro	Pro	107	Lys	Lys	Lys	Lys	Lys	Lys	
	45	Arg	Arg	Arg	Lys	Lys								
	46	Leu	Leu	Leu	Leu	Leu								
	47	Leu	Leu	Leu	Leu	Leu								
	48	Ile	Ile	Ile	Ile	Ile								
	49	Tyr	Tyr	Tyr	Tyr	Tyr								
C D R 2	50	Leu	Leu	Leu	Ser	Ser								
	51	Val	Val	Val	Ala	Ala								
	52	Ser	Ser	Ser	Ser	Ser								
	53	Asn	Asn	Asn	Tyr	Tyr								
	54	Leu	Leu	Leu	Arg	Arg								
	55	Glu	Glu	Asp	Tyr	Tyr								
	56	Ser	Ser	Ser	Thr	Thr								
	57	Gly	Gly	Gly	Gly	Gly								
	58	Val	Val	Val	Val	Val								
	59	Pro	Pro	Pro	Pro	Pro								
	60	Ala	Ala	Ala	Asp	Asp								
	61	Arg	Arg	Arg	His	Arg								
	62	Phe	Phe	Phe	Phe	Phe								
	63	Ser	Ser	Ser	Thr	Thr								
	64	Gly	Gly	Gly	Gly	Gly								
F R 3	65	Ser	Ser	Ser	Ser	Ser								
	66	Gly	Gly	Gly	Gly	Gly								
	67	Gly	Ser	Ser	Ser	Ser								
	68	Gly	Gly	Gly	Gly	Gly								
	69	Thr	Thr	Thr	Thr	Thr								
	70	Asp	Asp	Asp	Asp	Asp								
	71	Phe	Phe	Phe	Phe	Phe								
	72	Thr	Thr	Thr	Thr	Thr								
	73	Leu	Leu	Leu	Phe	Phe								
	74	Asn	Asn	Asn	Asn	Asn								
	75	Ile	Ile	Ile	Ile	Ile								
	76	His	His	His	His	His								
	77	Pro	Pro	Pro	Pro	Pro								
C D R 3	78	Val	Val	Val	Val	Val								
	79	Glu	Glu	Glu	Glu	Glu								
	80	Glu	Glu	Glu	Glu	Glu								
	81	Glu	Glu	Glu	Glu	Glu								
	82	Asp	Asp	Asp	Asp	Asp								
	83	Ala	Ala	Ala	Ala	Ala								
	84	Ala	Ala	Ala	Ala	Ala								
	85	Thr	Thr	Thr	Thr	Thr								
	86	Tyr	Tyr	Tyr	Tyr	Tyr								
	87	Tyr	Tyr	Tyr	Tyr	Tyr								
	88	Cys	Cys	Cys	Cys	Cys								
	89	Gln	Gln	Gln	Gln	Gln								
	90	His	His	His	His	His								
F R 4	91	Ile	Ile	Ile	Ile	Ile								
	92	Arg	Arg	Glu	Tyr	Tyr								
	93	Val	Gly	Gly	Ser	Ser								
	94	Ala	Ala	Ala	Pro	Thr								
	95	---	---	---	---	---								
	95A	---	---	---	---	---								
	95B	---	---	---	---	---								
	95C	---	---	---	---	---								
	95D	---	---	---	---	---								
	95E	---	---	---	---	---								
	95F	---	---	---	---	---								
	96	Tyr	Tyr	Tyr	Tyr	Tyr								
	97	Thr	Thr	Thr	Thr	Thr								
C D R 4	98	Phe	Phe	Phe	Phe	Phe								
	99	Gly	Gly	Gly	Gly	Gly								
	100	Gly	Gly	Gly	Gly	Gly								
	101	Gly	Gly	Gly	Gly	Gly								
	102	Thr	Thr	Thr	Thr	Thr								
	103	Lys	Lys	Lys	Lys	Lys								
	104	Leu	Leu	Leu	Leu	Leu								
	105	Glu	Glu	Glu	Glu	Glu								
	106	Ile	Ile	Ile	Ile	Ile								
	106A	---	---	---	---	---								
	107	Lys	Lys	Lys	Lys	Lys								



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 5683

DOCUMENTS CONSIDERED TO BE RELEVANT																		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)															
A	US-A-5 208 146 (R. ERIE) * the whole document * ---	1-27	C12N15/13 C07K16/42															
A	WO-A-89 00050 (AKZO NV) * claims * * examples * ---	1-27																
A	WO-A-93 10221 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) * the whole document * ---	1-27																
A	EUROPEAN JOURNAL OF CANCER AND CLINICAL ONCOLOGY, vol.24, no.5, May 1988, OXFORD, GB pages 829 - 838 Y. AOTSUKA ET AL. 'Identification of a malignant cell associated antigen recognized by a human monoclonal antibody.' * abstract * ---	1-27																
A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol.80, no.20, October 1983, WASHINGTON DC, USA pages 6327 - 6331 M. GLASSY ET AL. 'UC 729-6, a human lymphoblastoid B-cell line useful for generating antibody-secreting human-human hybridomas.' * abstract * ---	1-27	C12N C07K															
<p>The present search report has been drawn up for all claims</p> <table border="1"> <tr> <td>Place of search</td> <td>Date of completion of the search</td> <td>Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>16 March 1995</td> <td>Nooij, F</td> </tr> <tr> <td colspan="3">CATEGORY OF CITED DOCUMENTS</td> </tr> <tr> <td colspan="3"> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document </td> </tr> <tr> <td colspan="3"> T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	16 March 1995	Nooij, F	CATEGORY OF CITED DOCUMENTS			X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		
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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim							
A	<p>CANCER RESEARCH, vol.52, no.9, 1 May 1992, PHILADELPHIA PA, USA pages 2603 - 2609 W. TADDEI-PETERS ET AL. 'Quantitation of human tumor-reactive monoclonal antibody 16.88 in the circulation and localization of 16.88 in colorectal metastatic tumor tissue using murine antiidiotypic antibodies.' * abstract *</p> <p>---</p>	1-27							
P, A	<p>MOLECULAR IMMUNOLOGY, vol.30, no.16, November 1993, OXFORD, GB pages 1481 - 1489 K. YAGO ET AL. 'Immunoglobulin variable region sequences of two human monoclonal antibodies directed to an onco-developmental carbohydrate antigen, lactotetraosylceramide (LcOse4Cer).' * abstract *</p> <p>-----</p>	1-27							
			TECHNICAL FIELDS SEARCHED (Int.CI.)						
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